# *P*-Stereogenic, Bicyclic Phosphorus Heterocycles and Temporary Tether Strategies for the Synthesis of Complex Polyols

By

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# *P*-Stereogenic, Bicyclic Phosphorus Heterocycles and Temporary Tether Strategies for the Synthesis of Complex Polyols

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**Abstract**

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The development of atom-, redox-, and step-, and pot-economonical strategies for the streamlined synthesis of biologically active small molecules stands at the forefront of modern-day organic synthesis and early-stage drug discovery. In particular, those approaches that employ methods which allow for the reliable, predictable, and high-yielding coupling of a variety of both simple and elaborate chemical fragments to common core structural motifs represent some of the most efficient and versatile strategies to accomplish this goal. Since its first report in 2005, the use of phosphate triesters as temporary tethers has proven to be a powerful method for the facile formation of complex 1,3-skipped polyol-containing small molecules and biologically active natural products. The ability of phosphate tethers to impart differential olefin reactivity (exocyclic versus endocyclic), serve as temporary protecting groups, as well as latent leaving groups, and mediate several reactions in one-pot, sequential reactions continues to provide unique reactivity pathways to stereochemically rich intermediates, while minimizing chemical waste and the need for time-consuming purification. To date, phosphate-tether methods have served as the cornerstone in the total syntheses of dolabelide C, tetrahydrolipstatin, strictifolione, and Sch-725674, the formal synthesis of salicylihalimide A, and synthetic efforts toward lyngbouilloside and spirastrellolide B. Current efforts in the

group are focused on the expansion and diversification of phosphate tether-mediated RCM strategies for the two-directional synthesis of biologically active small molecules.

This thesis is dedicated to describing synthetic studies that augment previous work reported by our group involving *P*-stereogenic bicyclic phosphorus heterocycles and temporary tether strategies for the synthesis of complex polyols. Chapter 2 outlines a detailed study on the effects of stereochemical complexity, ring size, and olefin substitution on phosphate tether-mediated RCM. Studies focus on the formation of bicyclo[4.3.1]-, bicyclo[5.3.1]-, bicyclo[7.3.1]-, and bicyclo[8.3.1]phosphates, with a special emphasis on the factors that affect the success and stereochemical outcome of the *P*-tether mediated RCM event to form 10- and 11-membered bicyclic phosphates. Chapter 3 focuses on the synthesis of *P*-stereogenic bicyclo[4.3.1]phosphite-borane systems for the two-directional synthesis of complex polyols. These studies highlight the *P*-tether systems' ability to facilitate chemoselective olefin functionalization, divergent oxidation strategies that allow access to the corresponding phosphate or thiophosphate, and a stereocontrolled, iterative $S_N2'$-cuprate displacement protocol that marries the chemistry of phosphite borane tethers with that of their all oxygen-containing counterparts to generate polyol stereotetrads that were previously inaccessible via phosphate tether strategies alone. Chapter 4 presents the application of phosphate tether-mediated, one-pot sequential processes toward the total synthesis of 2*S*-sanctolide A and outlines plans for the application of the method to the total synthesis of 2*R*-sanctolide A and its analogs.

*To every little girl who prefers to dance through the aisles at the grocery store and live in a world of her own making.*

*And to the parents who let her—mine, in particular.*

**Acknowledgments**

From the girl who always talked too much, trust that there's something inherently comical about the fact that I have no words to start expressing how incredibly grateful I am to a group of people who have had such an extraordinary impact on my life—both personal and academic. The whirlwind that is your last year of graduate school has a tendency to steal all of the good memories, all of the laughs, all of the celebrations, all of the one-on-one moments, and spin them in the air above your head just long enough to make your knees buckle and your eyes water when they finally come back down to hit you on your way out. As disorienting as it sounds, though, it's the best part about finishing something because you start to realize just how much you've grown and how much the people around you have helped you do that. So, in true Jana fashion, let's start from the beginning and hope I make it through the list without having to stop and get a tissue.

To the handful of exceptional high school teachers who taught me how to love learning and to long for a challenge: I'll never be able to repay you for that. Mr. Manuel, you are one of the best educators—and people—I have ever known. Thanks for taking the time to invest in me.

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To Professor Jeffery White: I hated P-Chem, but I loved having you as a teacher. The way you cared about students still astounds and inspires me. In fact, your

"final e-mail" has become somewhat standard for the way I wrap up semesters, and it reminds me just how lucky I was to have known you.

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To Susanthi: I miss you more than words can say. Thanks for being such a great mentor and friend. I know you're kicking butt and taking names as a new Professor and "safety enforcer" in Sri Lanka, and I look forward to the great career you have ahead of you. FYI: I expect lots of baby pictures when you and Rohan decide to start having children because we all know they're going to be *adorable*.

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be “Lyndsey’s sister,” and I’m totally okay with that. You’ll always be my favorite person. I love you to the moon and back.

To my brother, John: you’re the other half of my heart. No one can make me laugh like you, and I don’t think anyone ever will rival the hold you have on my affection. No matter how far apart we are, no matter how stressed we are, we’ll always find that one GIF of J-Lo getting slapped by Jane Fonda in “Monster-In-Law” and know that things will be all right.

Finally, to Mom and Dad: I am 100% sure that I would not still be here—breathing, working, *living*—without you. You are the very best parts of me; the rest is a work in progress. Thanks for every phone call, every midnight run to the ER, every hug, every “Buck up, Buttercup.” You are everything I’ve ever needed, and you’ve been spectacular at it. Thanks, for all of it, and though it’s terrible compensation, this thesis is dedicated to you.

And to my grandma, Leona Jones: Thanks for making me feel perfectly loved.

Always.

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Temporary Tether Strategies for the Synthesis of Complex Polyols

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## Abbreviations

| | |
|---|---|
| MeCN | acetonitrile |
| aq | aqueous |
| Bn | benzyl |
| BnBr | benzyl bromide |
| brsm | based on recovered starting material |
| 9-BBN | 9-borabicyclo(3.3.1)nonane |
| BOPCl | bis(2-oxo-3-oxazolidinyl)phosphonic chloride |
| *t*-BuOH | *t*-Butanol |
| $CHCl_3$ | chloroform |
| CuI | copper iodide |
| cat. | catalytic |
| COSY | correlation spectroscopy |
| C | carbon |
| $Cs_2CO_3$ | cesium carbonate |
| Cl | chlorine |
| CM | cross metathesis |
| CuBr | copper bromide |
| CuI | copper iodide |
| DABCO | 1,4-diazabicyclo[2.2.2]octane |
| DBU | 1,8-diazabicycloundec-7-ene |
| DCM ($CH_2Cl_2$) | dichloromethane |
| DCE | 1,2-dichloroethane |
| DIAD | diisopropyl azodicarboxylate |
| DIPEA/Hünig's base | *N*,*N*'-diisopropylethylamine |
| DMAP | 4-(dimethylamino)pyridine |
| $Me_2SO_4$ | dimethylsulfate |
| Et | ethyl |

| | |
|---|---|
| $Et_2O$ | diethyl ether |
| EtOAc | ethyl acetate |
| EDC (EDCI) | 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide |
| G-I | Grubbs' first generation catalyst |
| G-II | Grubbs second-generation catalyst |
| GC | gas chromatography |
| HG-II | Hoveyda-Grubbs second generation catalyst |
| HRMS | high resolution mass spectrometry |
| h | hours |
| Hz | hertz |
| IR | infrared radiation |
| *i*-Bu | isobutyl |
| *i*-Pr | isopropyl |
| LiOH | lithium hydroxide |
| LCMS | liquid chromatography–mass spectrometry |
| M | molarity |
| Me | methyl |
| MeOH | methanol |
| MeI | methyl iodide |
| Mmol | millimole(s) |
| MOM | methoxymethyl- |
| MsCl | methanesulfonyl chloride |
| $NaHCO_3$ | sodium bicarbonate |
| NMO | *N*-methylmorpholine-*N*-oxide |
| NMR | nuclear magnetic resonance |
| NIH | National Institute of Health |
| nBuLi | *n*-butyllithium |
| OMe | methoxy |
| *o*-NBSH | *o*-nitrobenzene sulfonyl hydrazine |

| | |
|---|---|
| PMB | *para*-methoxybenzyl |
| ppm | parts per million |
| Ph | phenyl |
| $PCy_3$ | tricyclohexylphosphine |
| PTSA | *p*-toluenesulfonic Acid |
| $K_2CO_3$ | potassium carbonate |
| RCM | ring closing metathesis |
| rt | room temperature |
| sat. | saturated |
| NaO*t*Bu | sodium *tert*-Butoxide |
| NaHMDS | sodium hexamethyldisilazide |
| NaOH | sodium hydroxide |
| $Na_2SO_4$ | sodium sulfate |
| TBACl | tetrabutyl ammonium chloride |
| TBAF | tetrabutyl ammonium fluoride |
| TIPS | triisopropylsilyl- |
| TBDPS | *tert*-butyl(diphenyl)silyl- |
| TBS | *tert*-butyl(dimethyl)silyl- |
| TFA | trifluoroacetic acid |
| $K_3PO_4$ | tripotassium phosphate |
| $PPh_3$ | triphenylphosphine |
| TLC | thin layer chromatography |
| *t*-Bu | *tert*-butyl |
| $Et_3N$ | triethylamine |
| THF | tetrahydrofuran |
| 2,2-DMP | dimethoxypropane |
| PPTS | pyridinium p-toluenesulfonate |
| LLS | longest linear sequence |
| TSC | total step count |

# Chapter 1

*Recent Advances in Phosphate Tether-Mediated Strategies for the Two-Directional Synthesis of Natural Products*

## 1.1 Introduction

The development of step-, atom-, and redox-economical methods that allow for the facile formation of complex intermediates from simple starting materials is central to the design and execution of streamlined syntheses of biologically active small molecules, natural products, and natural product analogs.[1] In particular, temporary tether strategies, which can provide enhanced control of substrate reactivity and transformation selectivity through innate intramolecularity,[2] have served as powerful synthetic tools to accomplish this goal. While temporary silicon tethers are by far the most studied and well represented in the literature,[3] other tether systems, including ketal[4] and carboxylate tethers,[5] have been developed for intermediate coupling via ring-closing metathesis (RCM) olefination. Though every useful tether system will meet certain necessary requirements (i.e. high-yielding installation, stability to reaction conditions, easily removable),[2b] the benefit of additional synthetic utility, arising from the inherent chemical properties of the tether itself, magnifies the significance of the tool by allowing it to serve as a manipulatable functional handle for further diversification of substrates. In this regard, the ability of phosphate triesters to serve as tripodal tethers with the ability to act as both a protecting group and a latent leaving group capable of activating multiple carbinol centers to nucleophilic attack makes them intriguing targets for tether development. Moreover, in addition to their well-established reactivity profiles (Figure 1.1),[6] phosphates also possess a rich biological history—as phosphates are ubiquitous in nature[7] and are present in biologically active natural products,[8] as well as FDA-approved drugs and pro-drugs (Figure 1.2).[9] Thus, those intermediates that contain phosphate tether systems, obtained

*en route* to the total synthesis of a natural product or biologically active small molecule, may also possess interesting biological activity in their own right. For these reasons, the development of phosphate-based tripodal tether systems would be an attractive alternative to the more classically utilized divalent silicon systems.

**Figure 1.1** *Chemistry of phosphates.*

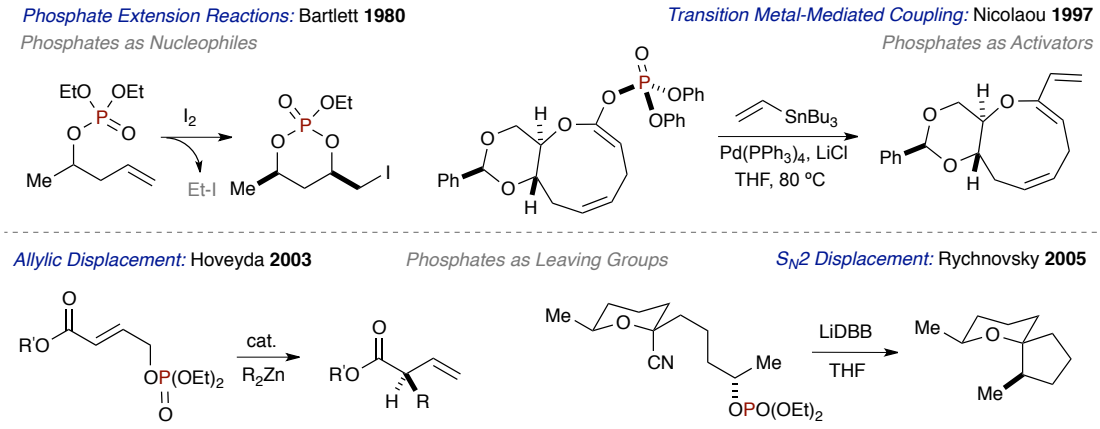
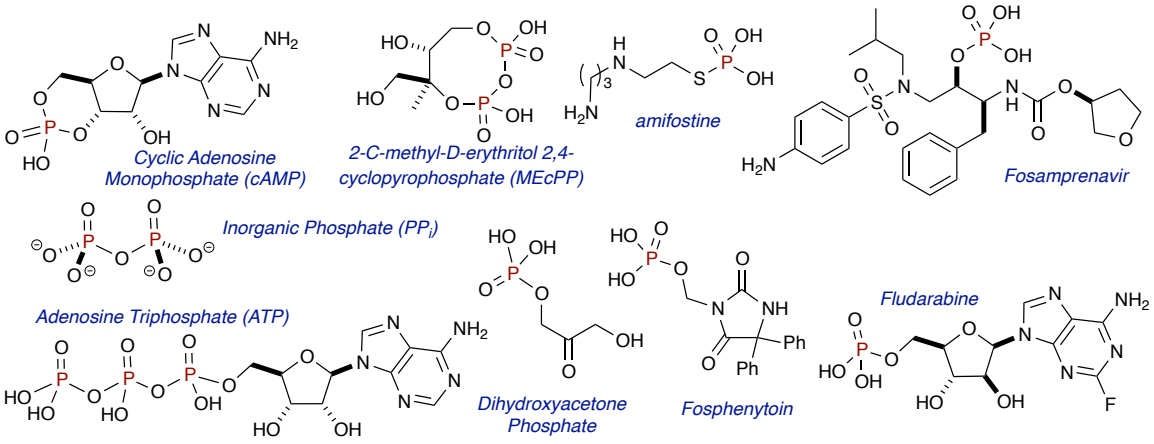
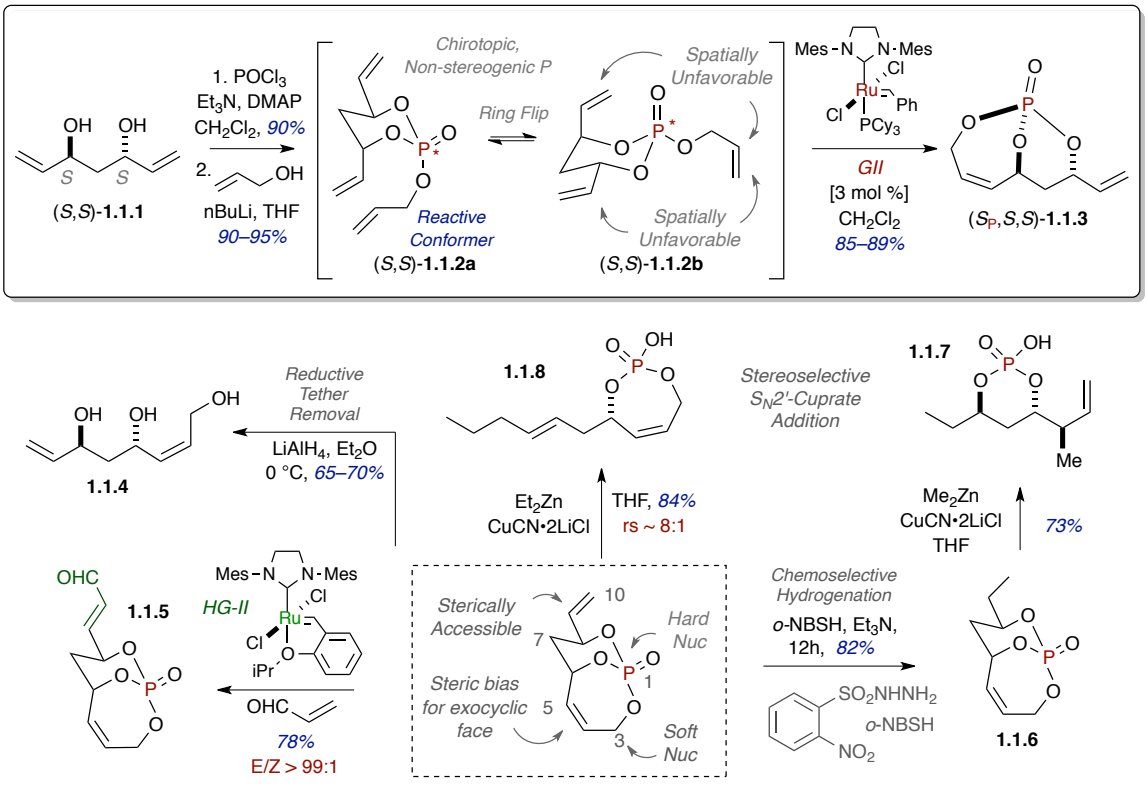



**Figure 1.2** *Phosphate-containing biologically active small molecules.*




In 2005, our group published the synthesis and reactivity of the first reported phosphate triester temporary tether strategy for the synthesis of 1,3-*anti*-diol-containing subunits (Scheme 1.1).[10] Condensation of (*S,S*)-dienediol **1.1.1**[11] [or the (*R,R*)-

enantiomer] with phosphorus(V) oxychloride ($POCl_3$), in the presence of triethylamine ($Et_3N$) and catalytic 4-dimethylaminopyridine (DMAP), provides the corresponding monocyclic, mono-chlorophosphate (not shown). Treatment of this unstable intermediate with the lithium alkoxide of allyl alcohol smoothly generates pseudo-$C_2$-symmetric phosphate triene (*S,S*)-**1.1.2**, which exists as two conformers (**1.1.2a** and **1.1.2b**, respectively). Subsequent ring-closing metathesis of triene **1.1.2**, facilitated by catalytic Grubbs second-generation catalyst [G-II, $(ImesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$],[12] then provides a single diastereomer of bicyclo[4.3.1]phosphate,[13] ($S_P$,*S,S*)-**1.1.3**, through reactive conformer (*S,S*)-**1.1.2a**.



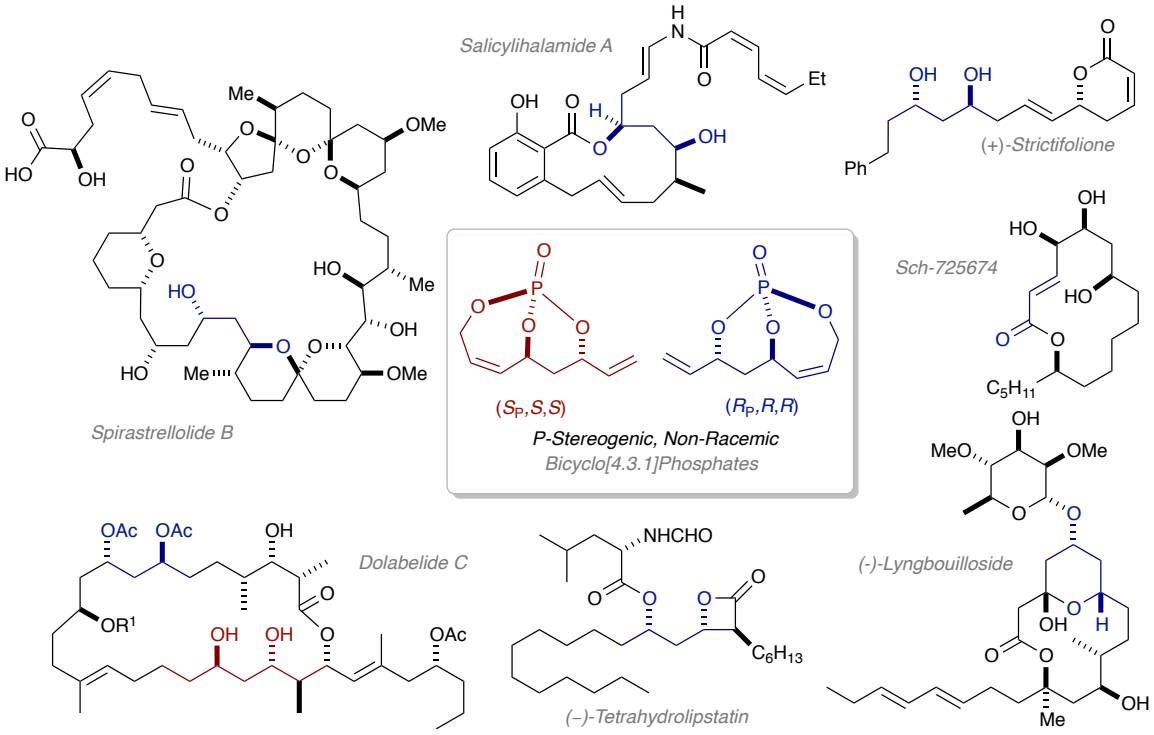

**Scheme 1.1** *Synthesis and reactivity of bicyclo[4.3.1]phosphates.*

The authors next sought to identify a basic reactivity profile for bicyclic phosphate **1.1.3**, which was found to be remarkably acid stable (up to 6 N HCl), as well as benchtop stable (>3 years). Reductive tether removal, by $LiAlH_4$, afforded triol **1.1.4** in good yield. Selective functionalization of the exocyclic olefin through cross metathesis (CM) with acrolein or hydrogenation via diimide reduction[14] generated functionalized systems **1.1.5** and **1.1.6** in 78% and 82% yields, respectively (Scheme 1.1). Stereoselective $S_N2'$-cuprate displacement of the phosphate tether in **1.1.6** provided 6-membered monocyclic phosphoric acid **1.1.7** in excellent yield and selectivity through C5-addition. Complementarily, $S_N2'$-cuprate displacement of the phosphate tether in **1.1.3** afforded 7-membered monocyclic phosphoric acid **1.1.8** in excellent yield and good selectivity (rs ~8:1) via C10-addition to the exocyclic olefin. In addition to establishing method viability, this original publication highlighted the synthetic utility of the phosphate triester tether and represented a solid platform upon which to expand the potential of the phosphate to serve as both a temporary tether and latent functional handle for subsequent substrate diversification.

Over the past 10 years, on-going efforts in our group have sought to exploit the inherent properties of phosphate triesters to develop tripodal *P*-tether systems for the generation of complex polyol-containing natural products.[15] This chapter will review recent advances in this methodology and its application in the synthesis of biologically active small molecules and natural product analogs (Figure 1.3). In particular, the ability of phosphate tethers to mediate several transformations in one-pot sequential processes will be highlighted. All in all, this chapter will seek to provide the reader with the

sufficient context necessary to fully understand how the work presented hereafter (Chapters 2-4 of this thesis) contributes to the on-going narrative within the field regarding *P*-stereogenic, bicyclic phosphorus heterocycles and temporary tether strategies for the synthesis of complex polyol-containing natural products.

**Figure 1.3** *Phosphate tether-mediated synthetic strategies toward the total synthesis of natural products.*

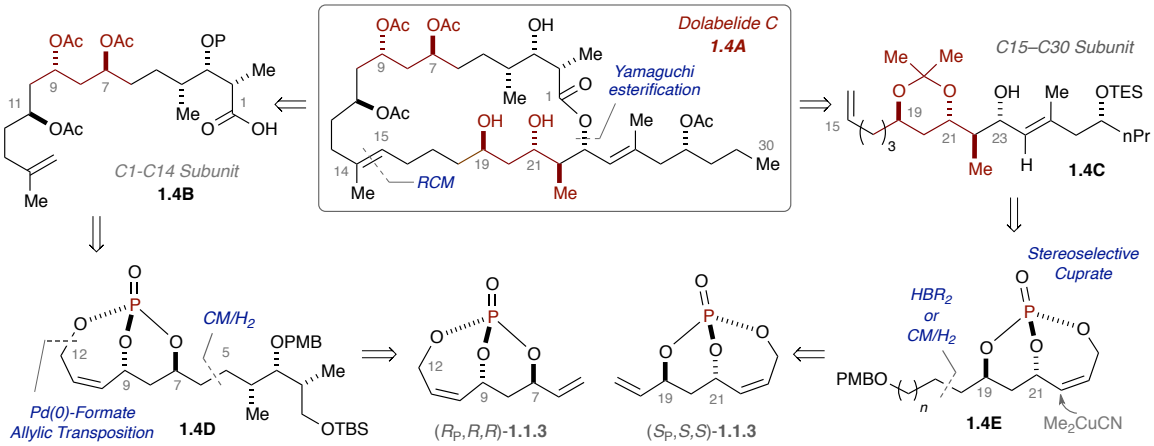



Because the earliest syntheses completed in our laboratory have been previously reviewed,[16] these works—the syntheses of dolabelide C, salicylihalimide A, and (–)-tetrahdrolipstatin—will be briefly reviewed with particular focus on those fragments assembled primarily by phosphate tether methods.

## 1.2 Total Synthesis of Dolabelide C

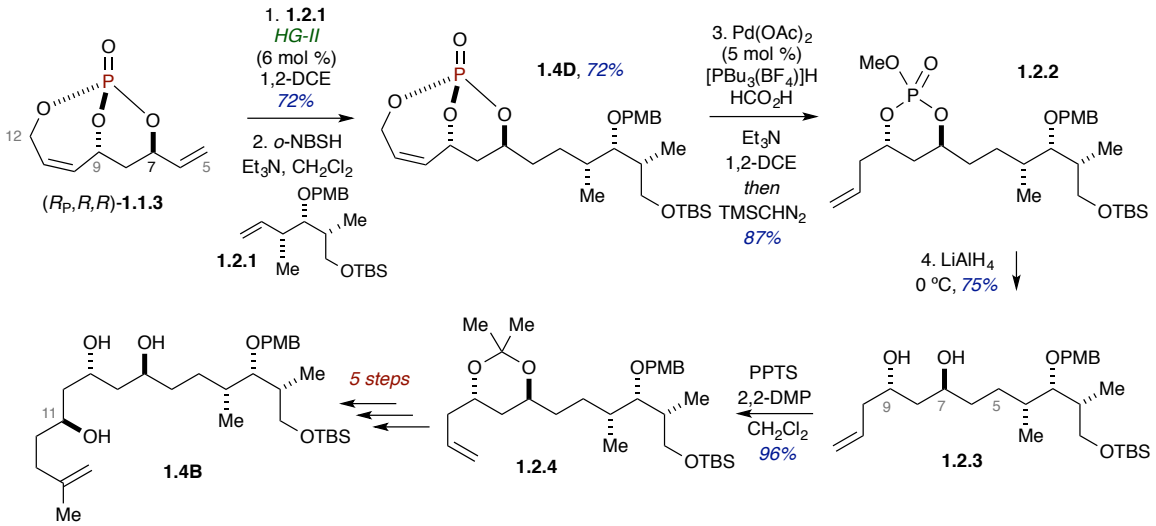
Dolabelide C (**1.4A**), a 24-membered, cytotoxic macrolide, was isolated and fully characterized in 1997 from the sea hare *Dolabella auricularia* by Yamada and coworkers (Figure 1.4).[17] Inspired by its stereochemical complexity and potent biological activity, our group targeted the total synthesis of dolabelide C, which culminated in three separate publications—the western portion (C1–C14)[18] and the eastern portion (C15–C30)[19] in 2008, followed by the total synthesis in 2011.[20] The retrosynthetic analysis involved a late-stage, macrocyclic ring-closing metathesis, preceded by a Yamaguchi esterification[21] to couple the two main fragments **1.4B** and **1.4C**, which would be generated via two separate synthetic strategies starting from both enantiomeric bicyclic phosphates **1.1.3**. For the western fragment (C1–C14), stereochemistry would be introduced using a cross-metathesis/hydrogenation pathway to provide **1.4D**, followed by a regioselective Pd-mediated allylic transposition of the bicyclic phosphate. For the eastern fragment (C15–C30), another cross-metathesis/hydrogenation protocol would install the long-chain alkenyl group (C15–C19), and a regio- and diastereoselective $S_N2'$-cuprate addition to

**Figure 1.4** *Retrosynthetic analysis to dolabelide C.*



intermediate **1.4E** would generate the methyl group at C22 and a terminal olefin for further functionalization.

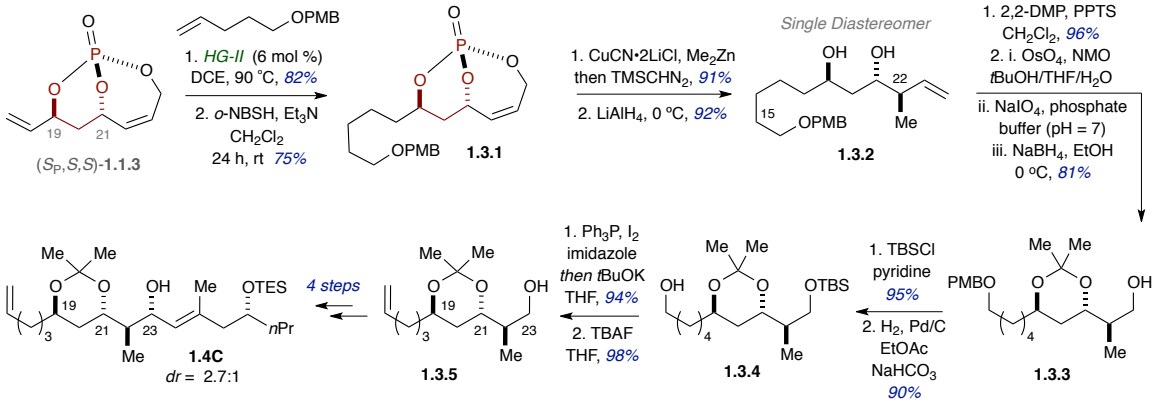
The synthesis of **1.4B** commenced with the coupling of ($R_P$,*R*,*R*)-**1.1.3** with olefin-containing stereotriad **1.2.1** (4 steps from Roche ester),[18] in the presence of Hoveyda-Grubbs second-generation catalyst[22] (HG-II, 6 mol %) (Scheme 1.2). Subsequent chemoselective hydrogenation of the exocyclic olefin, via diimide reduction,[14] in the corresponding cross-metathesis product provided **1.4D** in good overall yield. Allylic transposition of the bicyclic phosphate, followed by methylation of the resultant phosphoric acid, then afforded terminal olefin-containing monocyclic phosphate **1.2.2**, which was treated with $LiAlH_4$ to provide the corresponding diol in 75% yield. Acetal protection of the diol **1.2.3** with 2,2-dimethoxypropane and pyridinium *p*-toluene sulfonate generated **1.2.4** in 96%. Intermediate **1.2.4** was then converted into **1.4B** via a 5-step sequence involving ozonolysis of the terminal olefin, non-selective Grignard addition to the resultant aldehyde, and an oxidation-acetal deprotection-stereoselective




**Scheme 1.2** *Synthesis of the C1–C14 subunit of dolabelide C.*

reduction protocol to install the appropriate stereochemistry of the C11-alcohol.[18]

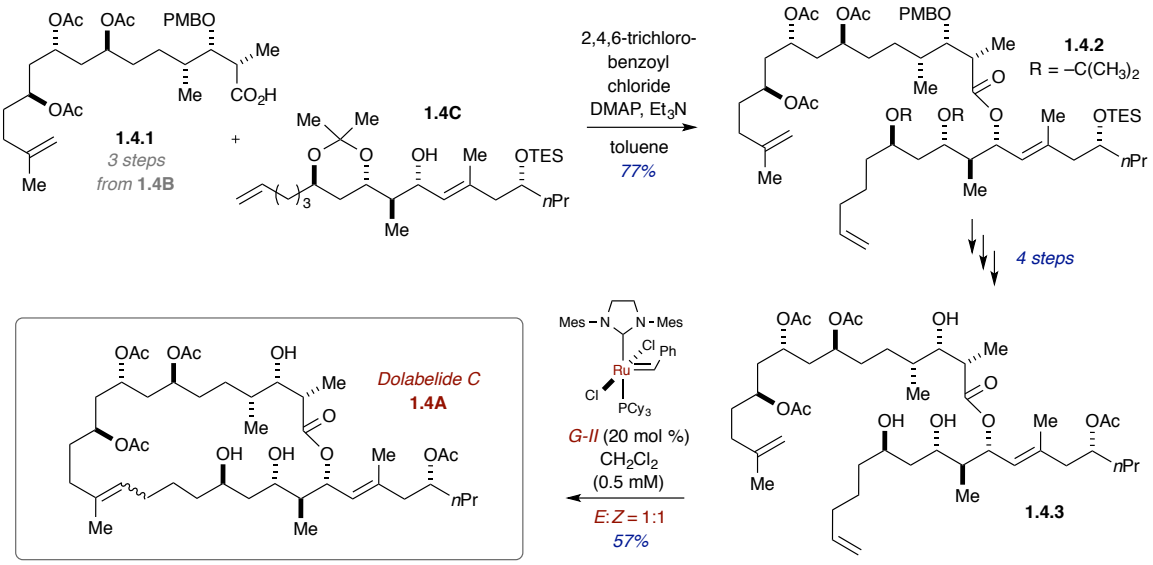
Likewise, the synthesis of fragment **1.4C** commenced with a second cross-metathesis/hydrogenation sequence (Scheme 1.3). In a similar manner as previously described, ($S_P$,*S*,*S*)-**1.1.3** and PMB-protected 4-penten-1-ol were treated with HG-II (6 mol %), followed by chemoselective hydrogenation of the resultant exocyclic olefin, to afford bicyclic phosphate **1.3.1** in good overall yield. Treatment of **1.3.1** with *in-situ*-generated dimethyl cuprate successfully installed the C22-methyl substituent with the appropriate stereochemical configuration via a regio- and diastereoselective $S_N2$'-cuprate displacement of the phosphate, and subsequent reductive tether removal generated the corresponding diol (**1.3.2**) in excellent yield. Acetal protection of diol **1.3.2** (96% yield), followed by Johnson-Lemieux oxidation of the terminal olefin and reduction of the resultant aldehyde with sodium borohydride, afforded primary alcohol **1.3.3** in 81% yield. Alcohol **1.3.3** was then TBS-protected and the distal hydroxyl group was PMB-deprotected with $H_2$, catalytic Pd/C, and sodium bicarbonate, in EtOAc, to provide




**Scheme 1.3** *Synthesis of C15–C30 fragment of dolabelide C.*

alcohol **1.3.4**. Alcohol **1.3.4** was converted to the primary alkyl iodide with triphenylphosphine ($PPh_3$) and $I_2$ and eliminated under basic conditions [potassium *tert*-butoxide (*t*BuOK)] to afford the corresponding terminal olefin (not shown). Subsequent TBS-deprotection of the resultant olefinic intermediate with TBAF furnished alcohol **1.3.5**, which was converted into intermediate **1.4C** over four steps.[20]

Finally, intermediate **1.4C** was coupled with acid **1.4.1**, which was obtained in 3 steps from intermediate **1.4B**, under conditions developed by Yamaguchi and coworkers, to provide **1.4.2** (Scheme 1.4).[21] Functional group interconversion over 4 steps generated diene **1.4.3**, which was subjected to a variety of ring-closing metathesis conditions to generate the title natural product. Ultimately, it was found that treatment of **1.4.3** with G-II (20 mol %), in refluxing methylene chloride (0.5 mM) provided dolabelide C (**1.4A**) in an optimized yield of 57%, albeit as a 1:1 mixture of *E*- and *Z*-isomers. Unfortunately,



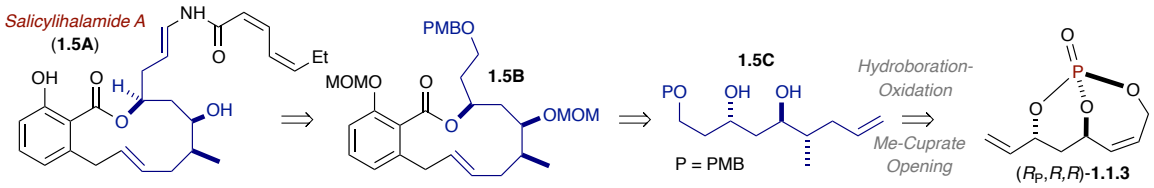

**Scheme 1.4** *End-game to dolabelide C and cross metathesis studies.*

this diastereomeric ratio was not improved through the use of alternative reaction conditions, though the advent of stereoselective metathesis catalysts[23] may provide a much-needed solution to the selectivity problem of this final macrocyclization step.

### 1.3 Formal Synthesis of (–)-Salicylihalimide A

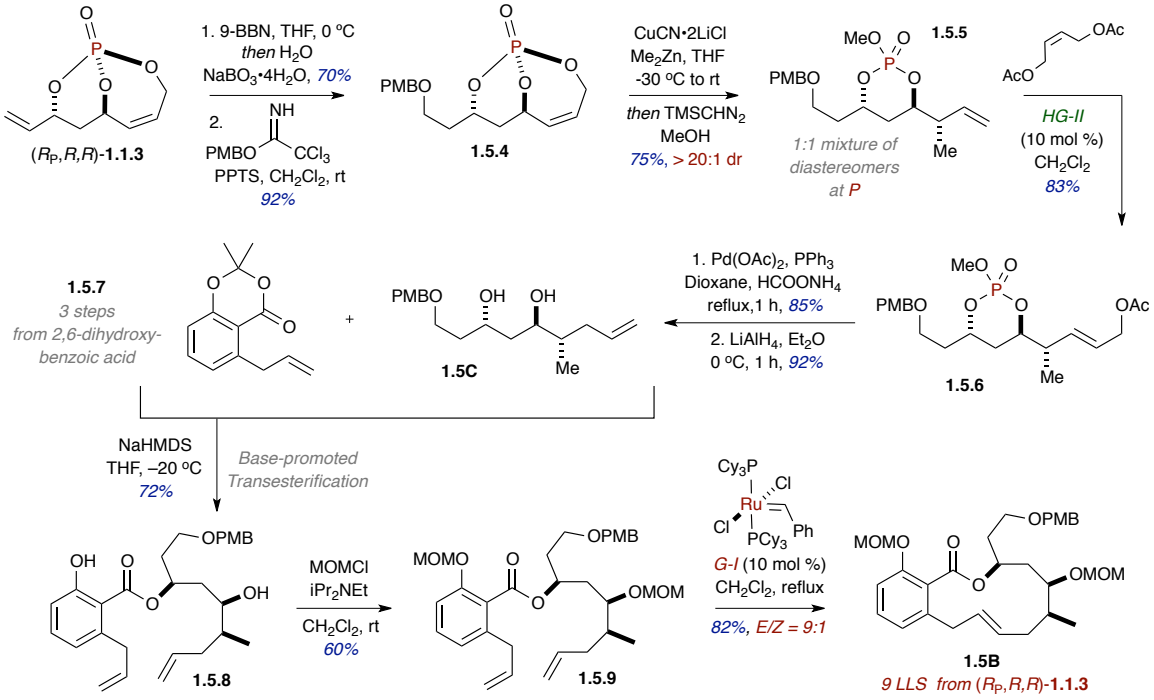
In 2011, Hanson and coworkers published the formal synthesis[24] of (–)-salicylihalimide A (**1.5A**), a cytotoxic macrolide isolated from marine sponge *Halicona* sp. in 1997 (Figure 1.5).[25] Retrosynthetic analysis revealed that **1.5A**, and its relative salicyclihalimide B,[25] could be obtained from distal functionalization of benzofused macrolactone **1.5B**. In turn, the stereochemically complex subunit in **1.5B**, simplified diol **1.5C**, could be derived from bicyclic phosphate ($R_P$,*R*,*R*)-**1.1.3** via a hydroboration-oxidation functionalization of the exocyclic olefin, followed by a regio- and diastereoselective $S_N2'$-cuprate addition to install the necessary branched methyl group and reveal a terminal olefin for further functionalization.

**Figure 1.5** *Retrosynthetic analysis of (–)-salicylihalimide A*




Following this strategy, ($R_P$,*R*,*R*)-**1.1.3** was hydroborated with 9-borabicyclo[3.3.1]nonane (9-BBN), followed by oxidation of the intermediate aliphatic borane, to provide the corresponding alcohol; *p*-methoxy-benzyl protection of the resultant alcohol afforded bicyclic phosphate **1.5.4** in 92% yield (Scheme 1.5). Treatment of **1.5.4** with *in-situ*-generated dimethyl cuprate, followed by methylation of the resultant

phosphoric acid, provided monocyclic **1.5.5** in 75% yield, as a 1:1 mixture of diastereomers at phosphorus. Subsequent cross-metathesis of **1.5.5** with *cis*-1,4-diacetoxy-2-butene generated allyl-acetate-functionalized intermediate **1.5.6**. Pd-mediated allylic transposition of the allyl acetate moiety in **1.5.6**, followed by reductive removal of the monocyclic phosphate, generated the corresponding diol (**1.5C**) in excellent yield. Base-promoted transesterification of intermediate **1.5.7**, obtained in 3 steps from commercially available 2,6-dihydroxy-benzoic acid,[26] with the alkoxide of **1.5C** provided the desired ester **1.5.8** in 72% yield. MOM-protection of both the phenolic and aliphatic alcohols furnished intermediate **1.5.9**, which was treated with Grubbs first generation catalyst (G-I, 10 mol %) in refluxing methylene chloride to generate macrolactone core **1.5B** in 82% yield as a 9:1 mixture of *E*- and *Z*-isomers.



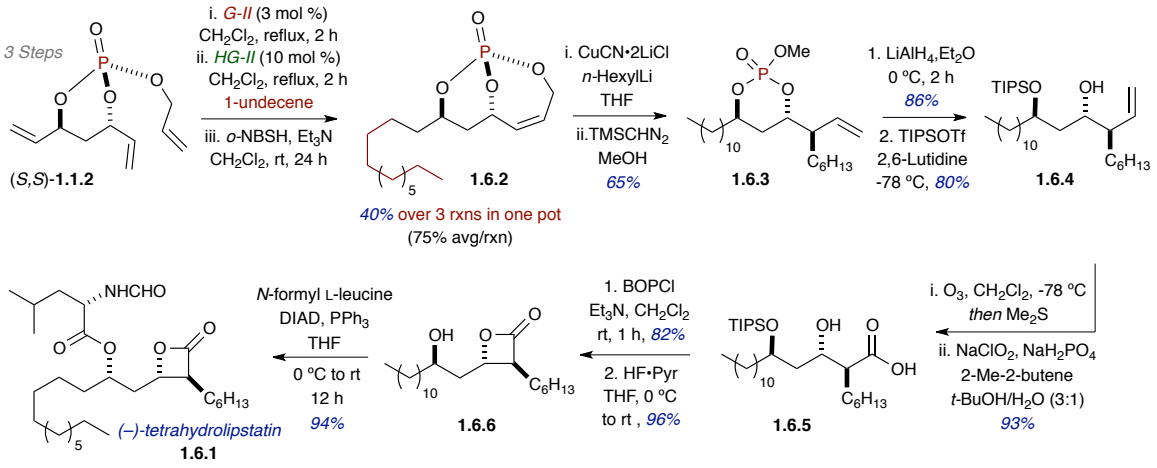

**Scheme 1.5** *Formal synthesis of (–)-salicylihalimide A.*

**1.4 Total Synthesis of (–)-Tetrahydrolipstatin:** *One-pot, Sequential RCM/CM/Hydrogenation*

In 2010, Hanson and coworkers reported the total synthesis of the anti-obesity drug (–)-tetrahydrolipstatin (**1.6.1**)[27] in a route consisting of 11-longest linear pots, including the first reported phosphate tether-mediated, one-pot sequential process—ring-closing metathesis/cross-metathesis/hydrogenation (Scheme 1.6).[28] Treatment of triene (*S,S*)-**1.1.2** with G-II (3 mol %), followed by addition of HG-II catalyst and olefinic cross-partner (1-undecene), then chemoselective diimide reduction (hydrogenation) of the exocyclic olefin, provided functionalized bicyclic phosphate **1.6.2** in 40% yield over 3 reactions in one pot (75% average per reaction). This one-pot, sequential process was optimized and the substrate scope expanded in a follow-up method development paper that was reported in 2012,[29] and it has served to streamline almost every synthetic effort towards other natural products and their analogs developed by our laboratory since its publication.

Bicyclic phosphate **1.6.2** was then treated with *in-situ*-generated dihexyl cuprate, followed by methylation of the resultant phosphoric acid, to provide monocyclic phosphate **1.6.3**, again as a 1:1 mixture of diastereomers at phosphorus (Scheme 1.6). Reductive tether removal, followed by TIPS-protection of the most sterically accessible secondary alcohol, afforded **1.6.4** in 85% and 80% yields, respectively. Subsequent ozonolysis and Pinnick oxidation[30] of the resultant aldehyde provided carboxylic acid **1.6.5** in excellent overall yield. β-Lactone formation was achieved by treating acid **1.6.5** with coupling reagent bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl) to

generate, after TIPS-deprotection with HF•pyridine, β-lactone **1.6.6**. Finally, coupling of **1.6.6** and *N*-formyl leucine, carried out under Mitsunobu conditions developed by Schneider,[31] afforded (–)-tetrahydrolipstatin (**1.6.1**) in 11-longest linear pots.

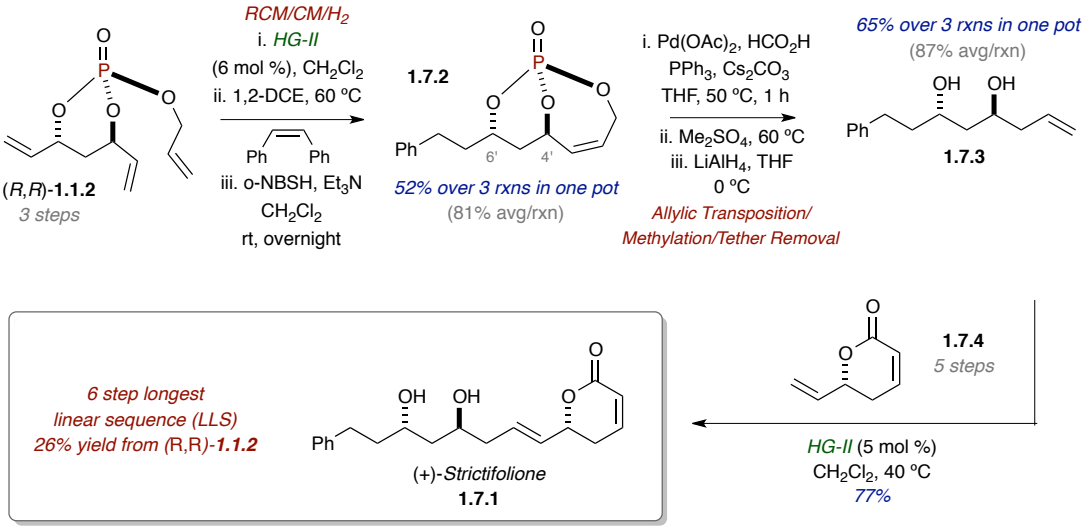



**Scheme 1.6** *Total synthesis of (–)-tetrahydrolipstatin.*

## 1.5 Total Synthesis of (+)-Strictifolione and (6*R*)-6[(*E*,4*R*,6*R*)-4,6-dihydroxy-10-phenyl-1-decenyl]-5,6-dihydro-2*H*-2-pyrone

The repertoire of phosphate tether-mediated, one-pot, sequential processes was expanded in application toward the streamlined and modular total synthesis of anti-fungal natural product (+)-strictifolione (**1.7.1**)[32] which was reported by our laboratory in 2014 (Scheme 1.7).[33] This synthetic strategy employed *two* one-pot, sequential processes to generate the title natural product in 6 longest-linear pots. Starting from triene (*R,R*)-**1.1.2**, one-pot RCM/cross metathesis (with *cis*-stilbene)/chemoselective hydrogenation (RCM/CM/hydrogenation) provided bicyclic phosphate **1.7.2** in 52% yield over 3 reactions (81% average per reaction). Pd-mediated, allylic transposition of the bicyclic phosphate in **1.7.2**, followed by methylation of the resultant phosphoric acid and

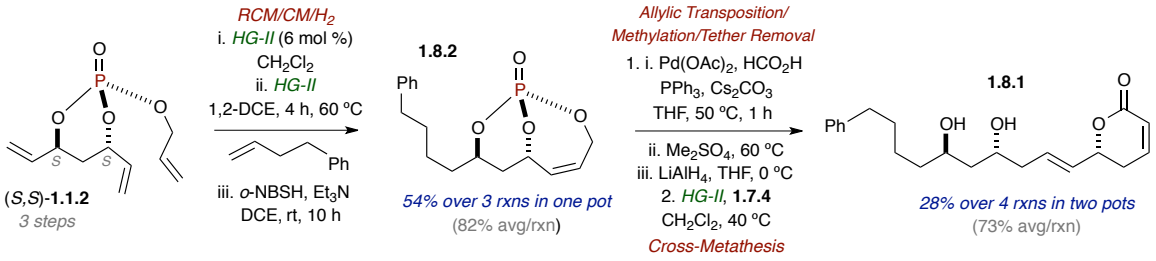
reductive tether removal with lithium aluminum hydride, afforded diol **1.7.3** in 65% over 3 reactions in one pot (87% average per reaction). Finally, diol **1.7.3** was coupled with α,β-unsaturated lactone **1.7.4** (5 steps from commercially available starting materials),[34] in the presence of HG-II (5 mol %) in refluxing methylene chloride, to provide (+)-strictifolione (**1.7.1**) in 77% yield, 26% overall yield from starting triene (*R,R*)-**1.1.2**.




**Scheme 1.7** *Total synthesis of (+)-strictifolione.*

In addition, a similar synthetic strategy was applied to the total synthesis of strictifolione relative (6*R*)-6[(*E*,4*R*,6*R*)-4,6-dihydroxy-10-phenyl-1-decenyl]-5,6-dihydro-2*H*-2-pyrone (**1.8.1**) (Scheme 1.8).[32c,d] A one-pot RCM/CM/hydrogenation protocol involving the coupling of the bicyclic phosphate resulting from RCM of triene (*S,S*)-**1.1.2** with but-3-en-1-ylbenzene provided functionalized bicyclic phosphate **1.8.2** in 54% yield over 3 reactions (82% average per reaction). Finally, intermediate **1.8.2** was converted to the natural product **1.8.1** via a two-pot procedure—a one-pot, sequential Pd-mediated allylic transposition/methylation/tether removal protocol, followed by cross-metathesis of

the intermediate olefinic alcohol with α,β-unsaturated lactone **1.7.4**.[34] Thus, the successful two-pot procedure provided (6*R*)-6[(*E*,4*R*,6*R*)-4,6-dihydroxy-10-phenyl-1-decenyl]-5,6-dihydro-2*H*-2-pyrone (**1.8.1**) from **1.8.2** in 28% yield over 2 steps and 4 reactions (73% yield average per reaction).

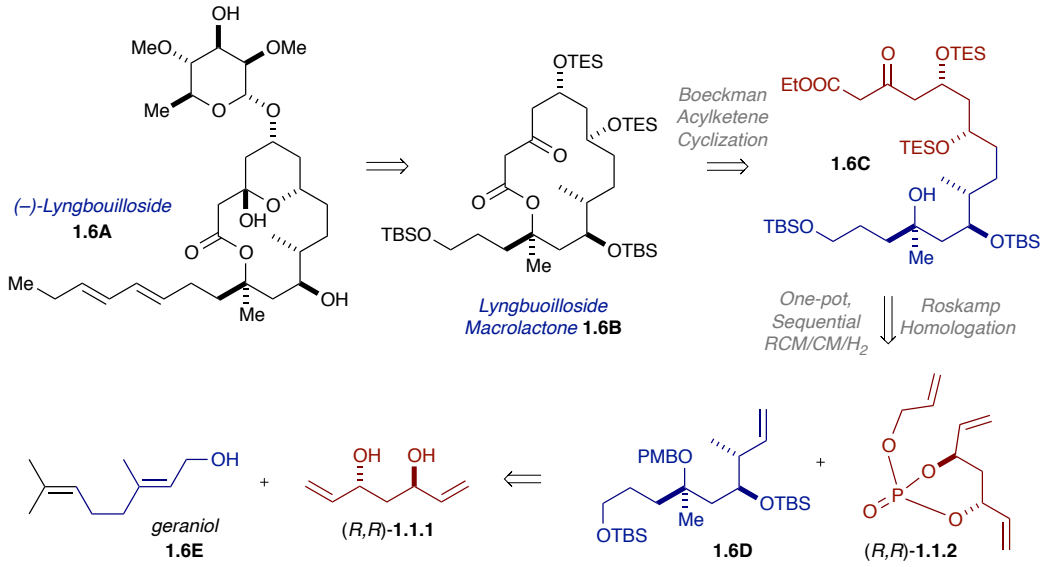



**Scheme 1.8** *Total synthesis of (6R)-6[(E,4R,6R)-4,6-dihydroxy-10-phenyl-1-decenyl]-5,6-dihydro-2H-2-pyrone.*

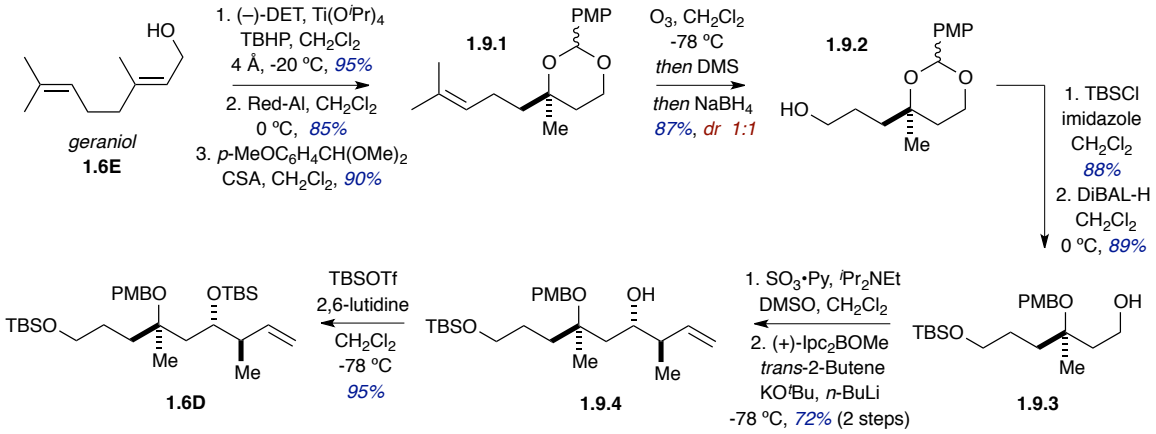
### 1.6 Synthesis of the Macrolactone Core of (–)-Lyngbouilloside

In 2015, Hanson and Chegondi reported synthetic efforts[35] toward (–)-lyngbouilloside (**1.6A**), a cytotoxic macrolactone isolated from marine cyanobacteria *Lyngbya bouillonii* in 2002 (Figure 1.6).[36] The authors proposed that the natural product could be obtained through an intermediate lactone core (**1.6B**), which was the primary target of the synthetic publication. In turn, macrolactone **1.6B** could be generated from a Boeckman acylketene cyclization[37] of β-ketoester **1.6C**, derived from the Roskamp homologation of the one-pot, sequential RCM/CM/hydrogenation product resulting from triene (*R,R*)-**1.1.2** and olefin **1.6D**. Finally, olefin **1.6D** could be synthesized from geraniol (**1.6E**), and (*R,R*)-**1.1.2** could be formed from the corresponding (*R,R*)-dienediol **1.1.1** in a one-pot, P(III)-coupling/oxidation strategy developed for the total synthesis of (–)-tetrahydrolipstatin.[28]

**Figure 1.6** *Retrosynthetic analysis to the macrolactone core of (–)-lyngbouilloside.*

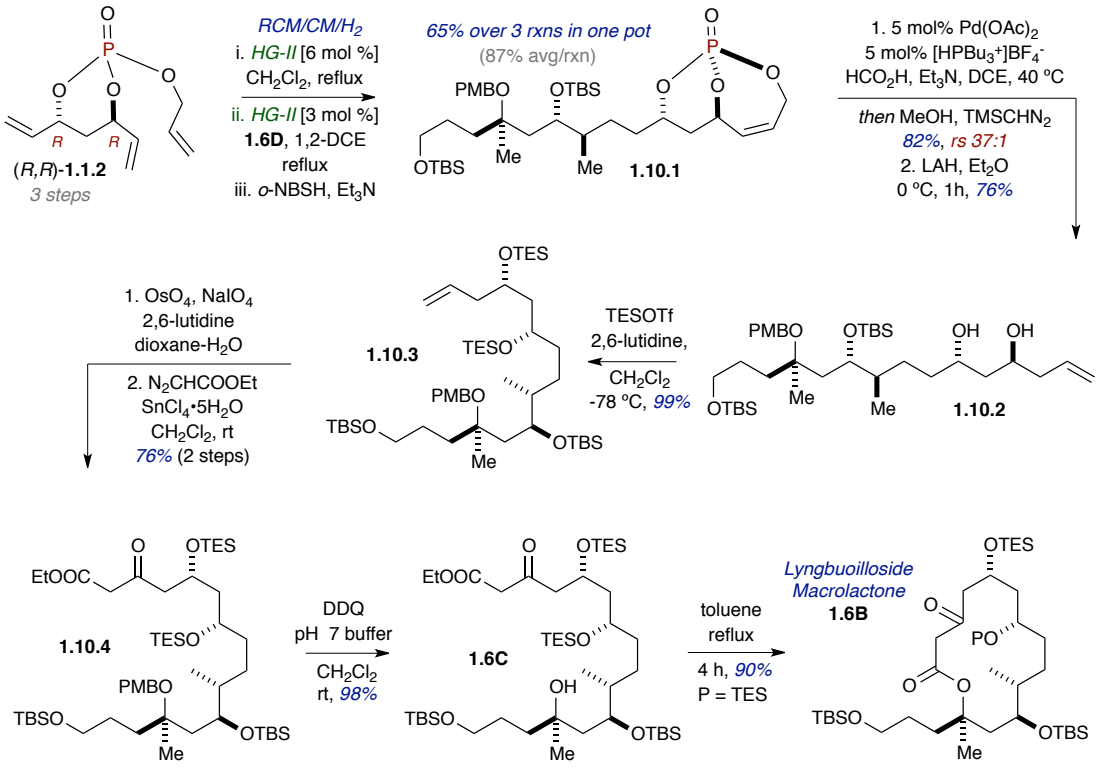



Thus, geraniol (**1.6E**) was exposed to allylic alcohol-directed Sharpless asymmetric epoxidation conditions[38] to provide the corresponding tri-substituted epoxide (not shown); subsequent regioselective, reductive epoxide opening with Red-Al, followed by PMP-acetal formation, provided intermediate **1.9.1** (Scheme 1.9). Ozonolysis of the trisubstituted olefin in **1.9.1**, followed by reduction of the resultant aldehyde, afforded primary alcohol **1.9.2** in 87% yield. TBS-protection of alcohol **1.9.2** and regioselective mono-deprotection of the PMP-acetal generated intermediate alcohol **1.9.3**. Parikh-Doering oxidation[39] of alcohol **1.9.3**, followed by Brown asymmetric crotylation[40] of the resultant aldehyde, furnished **1.9.4** in 72% yield over 2 steps. Finally, TBS-protection of the secondary alcohol in **1.9.4** with TBSOTf and 2,6-lutidine generated **1.6D** in 95% yield.




**Scheme 1.9** *Synthesis of C8–C16 fragment **1.6D**.*

Intermediate **1.6D** was then coupled with (*R,R*)-**1.1.2** in a one-pot, sequential RCM/CM/hydrogenation protocol (as previously described) to generate bicyclic phosphate **1.10.1** (Scheme 1.10). Regioselective, Pd-mediated allylic transposition of bicyclic phosphate **1.10.1**, followed by methylation of the resultant phosphoric acid and reductive tether removal of the corresponding monocyclic phosphate, afforded diol **1.10.2** in 82% and 76% yields, respectively (transposition-methylation and tether removal). The free alcohols were silyl-protected with TESOTf and 2,6-lutidine to generate intermediate **1.10.3** in excellent yield, and oxidative cleavage of the terminal olefin via a modified Johnson-Lemieux protocol[41] provided the corresponding aldehyde which was immediately subjected to a two-carbon Roskamp homologation,[42] with ethyl diazoacetate in the presence of $SnCl_4$•$5H_2O$, to furnish *β*-keto ester **1.10.4** in good overall yield. Finally, PMB-deprotection of the tertiary alcohol in **1.10.4** generated Boeckman cyclization precursor **1.6C**, which was cyclized in refluxing toluene to afford the target macrolactone in good overall yield.



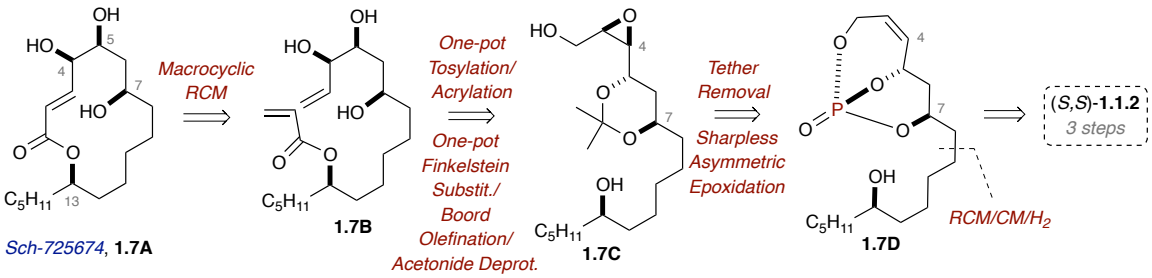

**Scheme 1.10** *Synthesis of lyngbouilloside macrolactone **1.6B**.*

## 1.7 Total Synthesis of Sch-725674

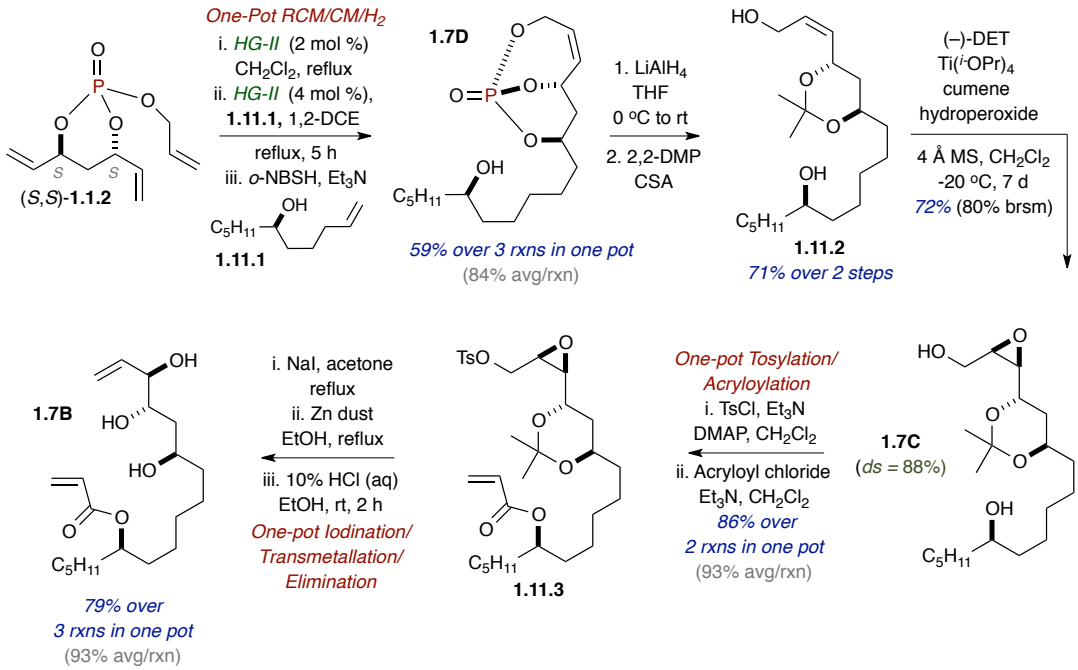
In 2016, Hanson and coworkers published a modular and pot-economical synthesis[43] of antifungal macrolide Sch-725674 (**1.7A**) that was isolated and characterized by Yang and coworkers in 2005.[44] Retrosynthetic analysis of **1.7A** showed that the natural product could be derived from the macrocyclic RCM of acyclic precursor **1.7B**, which could be generated from **1.7C** via *two*, one-pot, sequential processes: a one-pot tosylation of the primary alcohol and acryloylation of the secondary alcohol, followed by a one-pot Finkelstein substitution of the resultant primary tosylate, Boord olefination[45] of the intermediate alkyl iodide, and acetonide deprotection of the 1,3-*anti*-diol moiety. Correspondingly, epoxide **1.7C** could be formed from bicyclic phosphate **1.7D** via

reductive tether removal and Sharpless asymmetric epoxidation,[38] and **1.7D** would result from a one-pot sequential RCM/CM/hydrogenation protocol involving the appropriate olefinic alcohol and phosphate triene (*S,S*)-**1.1.2**.

**Figure 1.7** *Retrosynthetic analysis to Sch-725674.*

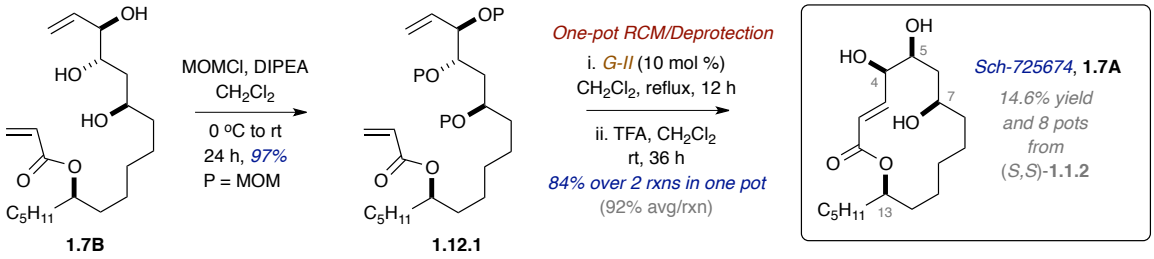



Following this approach, the authors first set out to synthesize **1.7B** (Scheme 1.11). Thus, phosphate triene (*S,S*)-**1.1.2** was coupled with olefinic alcohol **1.11.1** in a one-pot sequential RCM/CM/hydrogenation protocol similar to those previously described to provide functionalized bicyclic phosphate **1.7D** in 59% yield over 3 reactions in one pot (84% average per reaction). Reductive tether removal with $LiAlH_4$, followed by acetal protection of the 1,3-*anti*-diol moiety, afforded intermediate **1.11.2** in excellent yield over two steps. Alcohol-directed, asymmetric Sharpless epoxidation of allylic alcohol **1.11.2** provided the corresponding epoxide **1.7C** in good yield and diastereoselectivity. Subsequent one-pot tosylation of the most sterically accessible primary alcohol and acryloylation of the remaining secondary alcohol generated **1.11.3** in 86% yield over 2 reactions in one pot (93% average per reaction). Primary tosylate **1.11.3** was then treated with sodium iodide, in refluxing acetone (Finkelstein reaction), followed by Boord olefination[45] and acetal deprotection, to generate RCM-precursor **1.7B** in excellent 79% yield over three reactions in one pot (93% average per reaction).




**Scheme 1.11** *Synthesis of intermediate **1.7B**.*

Finally, though RCM of **1.7B** could provide the target of interest (**1.7A**, as previously reported),[46] it was found that global MOM-protection of triol **1.7B** significantly improved the efficiency of the final, macrocyclic RCM event. Thus, treatment of **1.7B** with MOM-Cl, in the presence of diisopropyl(ethyl)amine, provided **1.12.1** in excellent yield (97%), and subsequent one-pot sequential RCM/MOM-deprotection [G-II, *then* trifluoroacetic acid (TFA)] generated the natural product, Sch-725674, in 84% yield over two reactions in one pot (92% average per reaction) (Scheme 1.12). Overall, this strategy provided **1.7A** in 8 longest linear pots and 14.6% overall yield from triene (*S,S*)-**1.1.2**. In particular, this approach highlights the phosphate tether's ability to mediate a variety of transformations in one-pot sequential processes that allow for high-yielding, streamlined syntheses of natural products and natural product analogs.

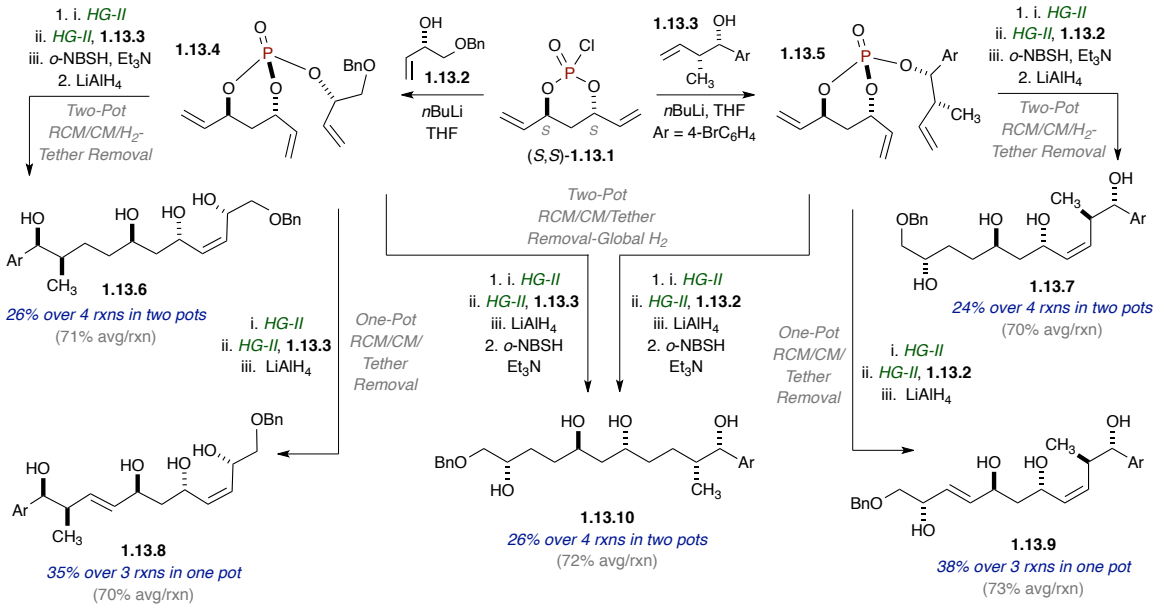



**Scheme 1.12** *End-game to Sch-725674 (**1.7A**).*

## 1.8 Pot-Economical Syntheses of 1,3-Skipped Polyols and α,β-Unsaturated Macrolactones

In addition to the synthesis of natural products, efforts in our laboratory have aimed at the development and expansion of known one-pot sequential pathways to generate natural-product-like libraries of small molecules. In 2014, Hanson and coworkers published a modular and divergent approach to the synthesis of 1,3-skipped polyols via a variety of one-pot sequential processes.[47] As shown in Scheme 1.13, coupling of mono-chlorophosphate (S,S)-**1.13.1** with either chiral, non-racemic olefinic alcohol **1.13.2** or **1.13.3** provided phosphate trienes **1.13.4** and **1.13.5**, respectively (Scheme 1.13). These substrates were then diversified utilizing three different pot-economical processes. The two-pot RCM/CM/hydrogenation-reductive tether removal strategy allowed for the coupling of triene **1.13.4** with olefinic alcohol **1.13.3** to afford tetraol **1.13.6** in 26% yield over 2 pots and 4 reactions (71% average per reaction). Similarly, triene **1.13.5** was coupled with olefinic alcohol **1.13.2** in a one-pot sequential RCM/CM/hydrogenation sequence, followed by reductive tether removal, to generate polyol **1.13.7** in 24% yield over 2 pots and 4 reactions (70% average per reaction). Conversely, triene **1.13.5** was again coupled with alcohol **1.13.3** in a one-pot, sequential

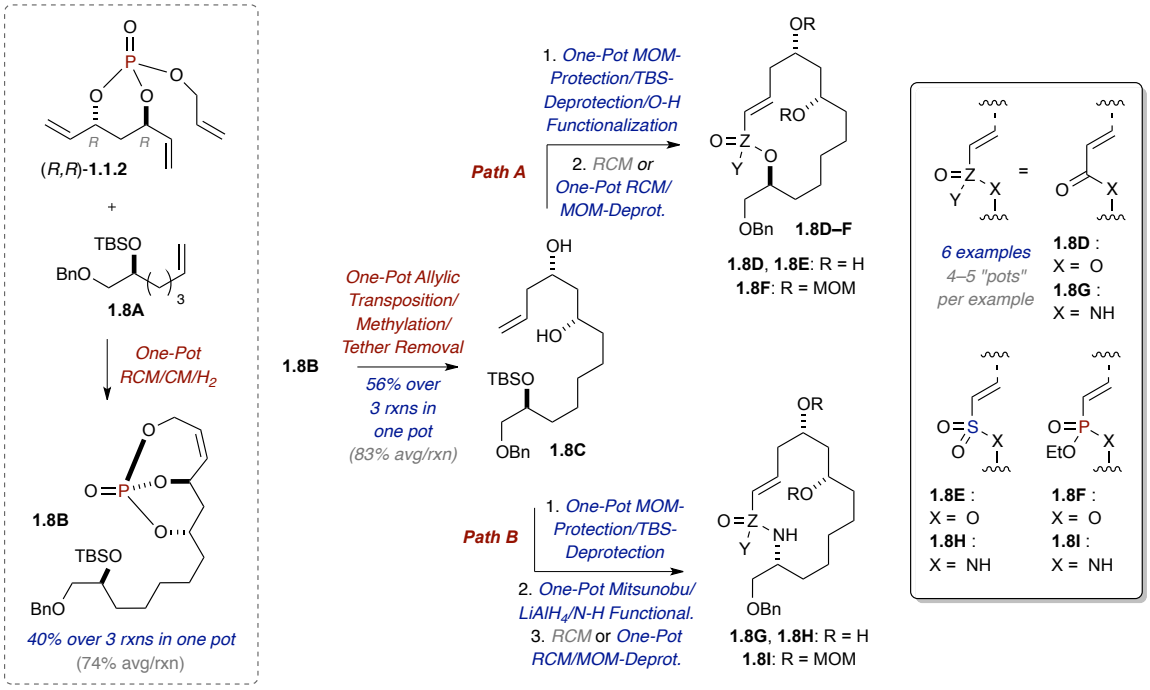
RCM/CM/tether removal protocol to provide polyol **1.13.8** in 35% yield over three reactions in one pot (70% average per reaction), and triene **1.13.5** was exposed to similar conditions—with addition of alcohol **1.13.2**—to afford polyol **1.13.9** in similar yield. Finally, two convergent, two-pot protocols involving a one-pot RCM/CM/tether removal, followed by global olefin reduction with *o*-NBSH and $Et_3N$, furnished tetraol **1.13.10** from either triene **1.13.4** or **1.13.5** (via the addition of the appropriate olefinic alcohol cross-partner). Taken collectively, these transformations highlighted the potential utility of one-pot sequential processes to provide diversified small molecule libraries from simple starting materials. In addition, this study served as an important basis set that legitimized further exploration and development of other phosphate tether-mediated, one-pot sequential processes for the facile formation of natural products.




**Scheme 1.13** *One-pot sequential strategies to 1,3-skipped polyols.*

Following the report of the total synthesis of macrolactone Sch-725674, in 2016, Hanson and coworkers published the synthesis of a small library of α,β-unsaturated macrolactones and macrolactone analogs via a series of one-pot sequential processes (Figure 1.8).[48] In a sequence reminiscent of those used in the previously reported synthesis of Sch-725674, a one-pot sequential RCM/CM/hydrogenation protocol coupled triene (*R,R*)-**1.1.2** with TBS-protected olefinic alcohol **1.8A** to provide intermediate **1.8B**, which was exposed to a one-pot sequential allylic transposition/methylation/tether removal (see the total synthesis of strictifolione, *vide supra*) to generate intermediate **1.8C**. This intermediate was then diversified via one of two pathways involving 2–3 one-pot sequential protocols to synthesize a library of 6, 14-membered macrocycles—

**Figure 1.8** *One-pot sequential strategies to α,β-unsaturated macrolactones.*



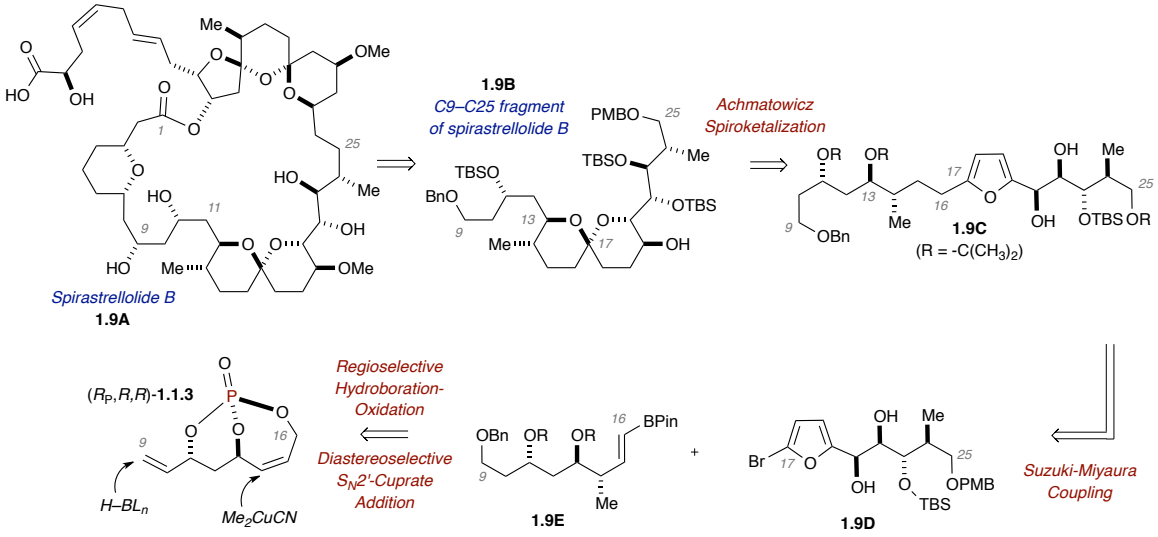
including lactones, lactams, sultones, sultams, phosphonates, and phosphonamides (**1.8D–I**, Figure 1.8). Thus, following Path A, **1.8C** was exposed to a one-pot sequential diol-protection with MOM-chloride and facilitating diisopropyl(ethyl)amine, de-silylation with TBAF, and *O*-functionalization (with acryloyl chloride, 2-chloroethanesulfonyl chloride, or ethyl(vinyl)phosphonochloridate[49]) to afford the corresponding dienes in 72–75% yield over 3 reactions in one-pot (60% yield for 3 reactions in 2 pots for **1.8F** diene). The dienes were then treated with G-II (10 mol %), and—in some cases—MOM-deprotection with HCl, to furnish final macrocycles **1.8D–F** in excellent overall yield. Similarly, following Path B, **1.8C** was transformed to macrolactam **1.8G**, macrosultam **1.8H**, and macrophostam **1.8I** via 3, one-pot sequential processes—including a one-pot Mitsunobu reaction with diphenylphosphorylazide, azide reduction with $LiAlH_4$, and amine functionalization (with acryloyl chloride, 2-chloroethanesulfonyl chloride, or ethyl(vinyl)phosphonochloridate). These investigations further illustrated the power of one-pot, sequential processes—including phosphate tether-mediated transformations—to generate structurally diverse libraries of natural product analogs in a modular fashion with minimal intermediate isolation/purification.

## 1.8 Efforts Toward the Total Synthesis of Spirastrellolide B: Phosphate Tether Strategies to the C9–C25 Fragment

In 2016, Hanson and coworkers reported efforts toward the synthesis of spirastrellolide B (**1.9A**),[50] a marine macrolide isolated from Caribbean marine sponge *Spirastrella coccinea* by Andersen and coworkers in 2007.[51] The authors proposed that the stereochemically rich C9–C25 fragment (**1.9B**) could be formed via an Achmatowicz

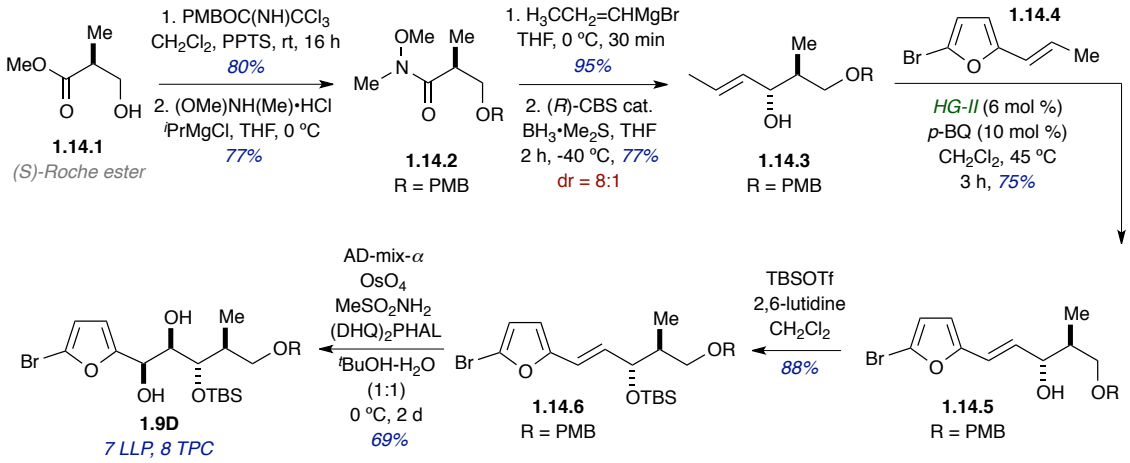
spiroketalization[52] of furan polyol **1.9C**, which, in turn, could arise from the Suzuki-Miyaura coupling of bromo-furan **1.9D** and vinyl-borane **1.9E** (Figure 1.9). 1,3-*Anti*-diol-containing intermediate **1.9E** could be synthesized from bicyclic phosphate (*R*P,*R*,*R*)-**1.1.3** via a regioselective hydroboration-oxidation of the exocyclic olefin and a diastereoselective $S_N2'$-addition of dimethyl cuprate to install the C14-methyl group.

**Figure 1.9** *Retrosynthetic analysis to spirastrellolide B.*




Synthesis commenced with the generation of intermediate **1.9D**. PMB-protection of the primary alcohol in (*S*)-Roche ester **1.14.1**, followed by Weinreb amide[53] formation with *N,O*-dimethylhydroxylamine•hydrochloride and iPr-MgCl, provided intermediate **1.14.2** in excellent overall yield (Scheme 1.14). Vinylation of **1.14.2**, carried out with 1-propenylmagnesium bromide, and subsequent Corey-Bakshi-Shibata reduction[54] of the resultant α,β-unsaturated ketone afforded chiral, non-racemic allylic alcohol **1.14.3** in 77% yield (dr = 8:1). Ruthenium-catalyzed cross-metathesis of **1.14.3** with 2-bromo-5-propenyl-furan (**1.14.4**, obtained in one step from 5-bromo-2-furaldehyde) furnished

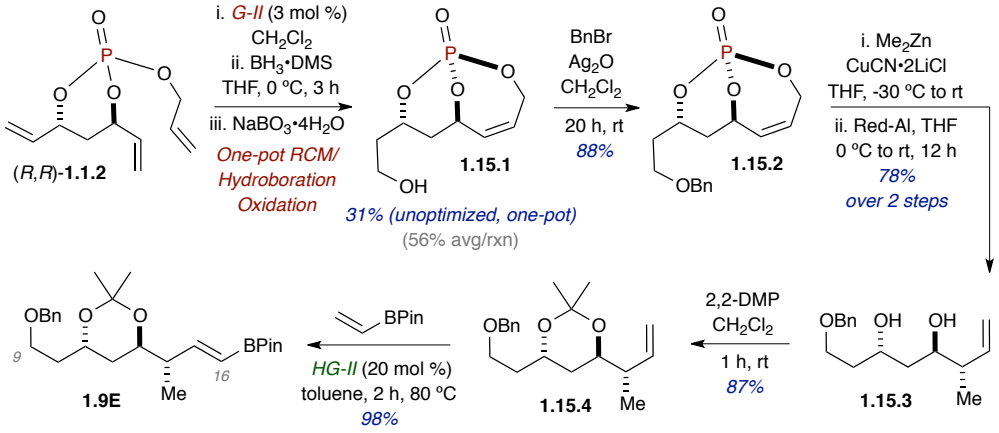
**1.14.5** in 75% yield. Subsequent TBS-protection of the allylic alcohol with TBSOTf and 2,6-lutidine, followed by Sharpless asymmetric dihydroxylation[55] of the internal olefin with AD-mix-α, osmium tetroxide, and hydroquinine 1,4-phthalazinediyl diether $(DHQ)_2PHAL$, in *tert*-butanol:water (1:1) at 0 °C, generated intermediate **1.9D** in 69% yield and 7 longest-linear pots (8 total pot count).




**Scheme 1.14** *Synthesis of intermediate **1.9D**.*

With **1.9D** in hand, the authors turned their sights to the generation of the second Suzuki-Miyaura coupling partner, intermediate **1.9E** (Figure 1.9). RCM of phosphate triene (*R,R*)-**1.1.2** with G-II (3 mol %), followed by chemoselective hydroboration of the resultant bicyclic phosphate with $BH_3$•DMS and oxidation with sodium perborate, afforded functionalized bicyclic phosphate **1.15.1** in 31% yield over 2 reactions in one pot (56% average per reaction, unoptimized). It should be noted that these individual steps were optimized and reported, as well (86% for the RCM, 84% for the hydroboration-oxidation sequence), though the one-pot process—even unoptimized—shows promise as a new means to further functionalize the bicyclic phosphate

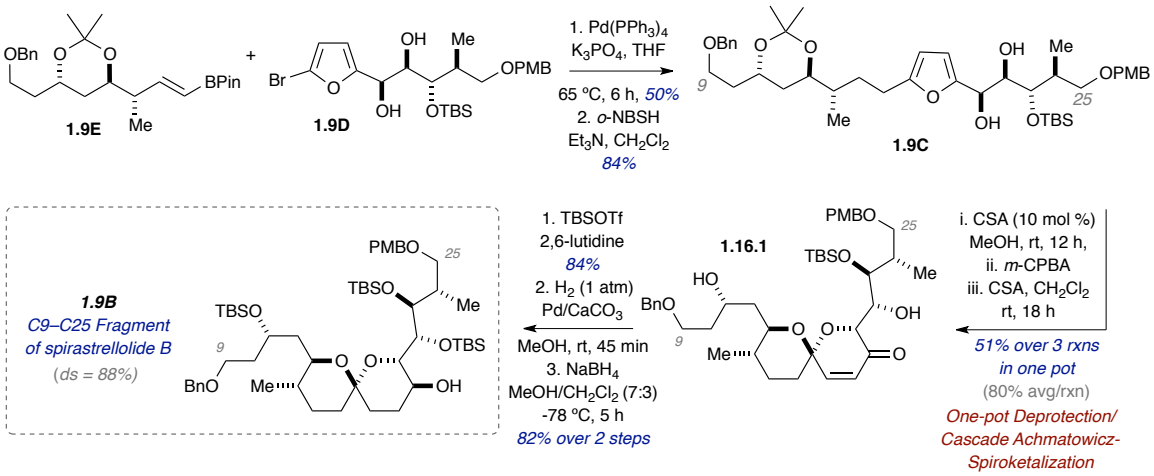
framework, which is why it is included here. Subsequent benzyl protection of the primary alcohol with BnBr and $Ag_2O$ afforded **1.15.2**, which was treated with *in-situ*-generated dimethyl cuprate, followed by reductive removal of the resultant phosphoric acid, to provide diol **1.15.3** and install the C14-methyl group with the appropriate stereochemical configuration. Diol **1.15.3** was acetal protected to generate **1.15.4** in 87% yield, and subsequent cross metathesis of **1.15.4** with commercially available pinacol vinylboronate successfully furnished intermediate **1.9E** in near quantitative yield (98%).




**Scheme 1.15** *Synthesis of intermediate **1.9E**.*

Finally, Suzuki-Miyaura coupling of vinylboronate **1.9E** with bromo-furan **1.9D**, with $Pd(PPh_3)$ and tripotassium phosphate base, provided the desired coupling partner (not shown) in the best—though still modest—yield (50%). Diimide reduction of the resultant olefin, with excess *o*-NBSH and $Et_3N$, generated Achmatowicz-cyclization precursor **1.9C** in 84% yield. Subsequent acetal deprotection with catalytic camphorsulfonic acid (CSA, 10 mol %), followed by cascade Achmatowicz-spiroketalization (*m*-CPBA, *then* CSA), afforded the desired spiroketal-containing diol **1.16.1** in 51% yield over 3 reactions in one pot (80% average per reaction). Finally,

global TBS-protection of **1.16.1** with TBSOTf and 2,6-lutidine, C=C double bond reduction with $H_2$ and Lindlar catalyst, and diastereoselective reduction (ds = 88%) of the resultant ketone provided the C9–C25 fragment of spirastrellolide B (**1.9B**) in good overall yield.




**Scheme 1.16** *Synthesis of C9–C25 fragment of spirastrellolide B.*

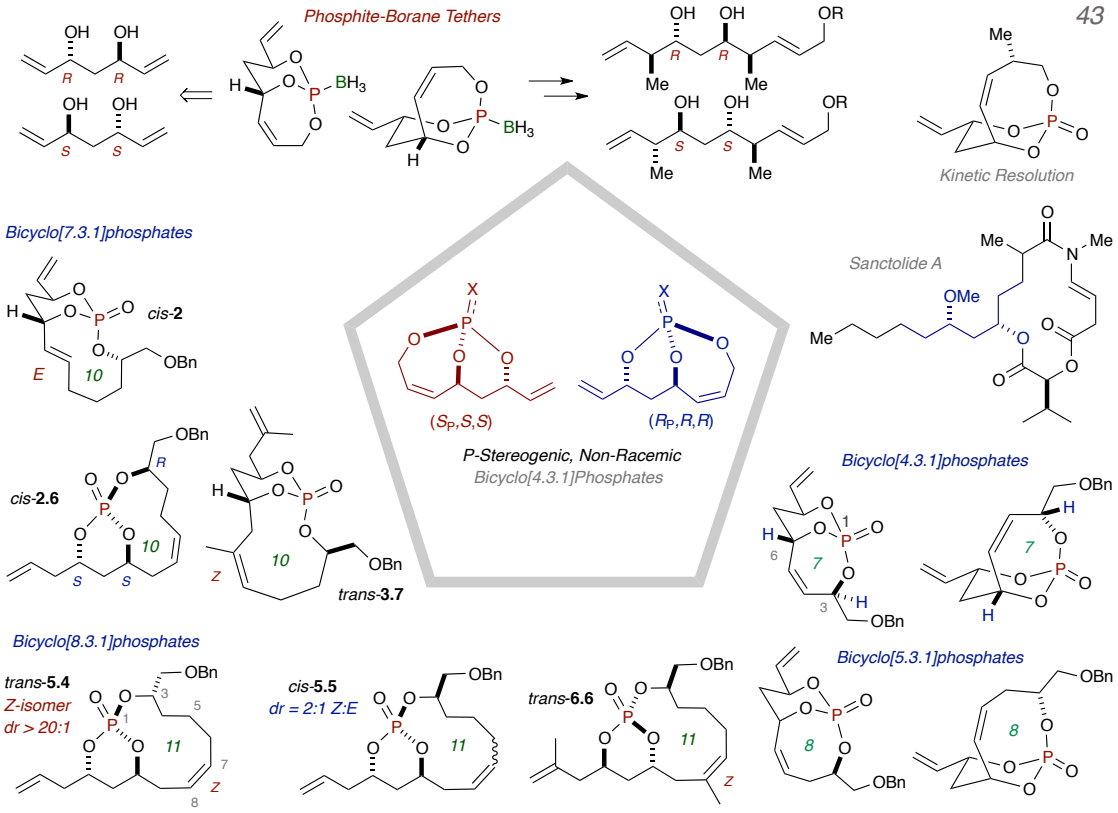
## 1.9 Conclusions

Since its first report in 2005, the use of phosphate triesters as temporary tethers has proven to be a powerful method for the facile formation of complex 1,3-skipped polyol-containing small molecules and biologically active natural products. The ability of phosphate tethers to impart differential olefin reactivity (exocyclic versus endocyclic) and serve as temporary protecting groups, as well as latent leaving groups, bolsters the synthetic utility of this tripodal tether system by allowing for the simple, modular diversification of common core intermediates to rapidly build molecular complexity. In addition, the ability of phosphate triester tethers to mediate several reactions in one-pot, sequential reactions continues to provide unique reactivity pathways to stereochemically

rich intermediates while minimizing chemical waste and the need for time-consuming purification. To date, phosphate-tether methods have served as the cornerstone in the total syntheses of dolabelide C, tetrahydrolipstatin, strictifolione, and Sch-725674, the formal synthesis of salicylihalimide A, and synthetic efforts toward lyngbouilloside and spirastrellolide B (*vide supra*), and current efforts in the group are focused on the expansion and diversification of phosphate tether-mediated, one-pot sequential processes for use in the streamlined synthesis of biologically active small molecules.

The remainder of this thesis is dedicated to describing synthetic studies that augment previous work outlined in this introductory chapter. These investigations include: (i) a detailed study on the effects of stereochemical complexity, ring size, and olefin substitution on phosphate tether-mediated RCM; (ii) the development of complementary phosphite-borane tether systems that can be used separately or in tandem with phosphate tethers to generate 1,3-skipped polyol stereotetrads that were previously inaccessible via phosphate tether methods alone; and (iii) the application of phosphate tether-mediated one-pot sequential processes toward the total synthesis of 2*S*-sanctolide A (Figure 1.10).

**Figure 1.10** *Preview abstracts outlining the work presented in this thesis.*



## 1.10 References Cited


[1] (a) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. Function-Oriented Synthesis, Step Economy, and Drug Design. *Acc. Chem. Res.* **2008**, *41*, 40–49; (b) Trost, B. M. Atom Economy – A Search for Synthetic Efficiency. *Science* **1991**, *254*, 1471–1477; (c) Trost, B. M. Atom Economy – A Challenge for Organic Synthesis: Homogeneous Catalysis Leads the Way. *Angew. Chem. Int. Ed.* **1995**, *34*, 259–281.

[2] For an excellent review on reversible, covalent bonding and induced intramolecularity as it relates to catalysis, see: Tan, K. L. *ACS Catal.* **2011**, *1*, 877–886.

[3] For a few great reviews on recent advances and applications of temporary silicon tethers in total synthesis, see: (a) Cusak, A. Temporary Silicon-Tethered Ring-Closing Metathesis: Recent Advances in Methodology Development and Natural Product Synthesis. *Chem. Eur. J.* **2012**, *18*, 5800–5824; (b) Bracegirdle, S.; Anderson, E. A. Recent Advances in the Use of Temporary Silicon Tethers in Metal-mediated Reactions. *Chem. Soc. Rev.* **2010**, *39*, 4114–4129; (c) Evans, P. A. Temporary Silicon-Tethered Ring-Closing Metathesis Reactions in Natural Product Synthesis. In *Metathesis in Natural Product Synthesis: Strategies, Substrates and Catalysts.* Cossy, J.; Arseniyadis, S.; Meyer, C., Eds.; Wiley-VCH: Weinheim, Germany, 2010; pp. 225–259.

[4] (a) Burke, S. D.; Muller, N.; Beaudry, C. M. Desymmetrization by Ring-Closing Metathesis Leading to 6,8-Dioxabicyclo[3.2.1]octanes: A New Route for the Synthesis of (+)-exo- and endo-Brevicomin. *Org. Lett.* **1999**, *1*, 1827–1829; (b) Burke, S. D.; Voight, E. A. Formal Synthesis of (+)-3-Deoxy-D-glycero-D-galacto-2-nonulosonic Acid (KDN) via Desymmetrization by Ring-Closing Metathesis. *Org. Lett.* **2001**, *3*, 237–240; (c) Voight, E. A.; Rein, C.; Burke, S. D. Synthesis of Sialic Acids via Desymmetrization by Ring-Closing Metathesis. *J. Org. Chem.* **2002**, *67*, 8489–8499; (d) Van Hooft, P. A. V.; Leeuwenburgh, M.

A.; Overkleeft, H. S.; Van Der Marel, G. A.; Van Boeckel, C. A. A.; Van Boom, J. H. A Novel and Flexible Synthesis of Pyranose Spiroacetal Derivatives. *Tetrahedron Lett.* **1998**, *39*, 6061–6064; (e) Scholl, M.; Grubbs, R. H. Total Synthesis of (–)- and (±)-Frontalin via Ring-Closing Metathesis. *Tetrahedron Lett.* **1999**, *40*, 1425–1428; (f) Ghosh, S. K.; Hsung, R. P.; Wang, J. Ketal-tethered Ring-Closing Metathesis. An Unconventional Approach to Constructing Spiroketals and Total Synthesis of an Insect Pheromone. *Tetrahedron Lett.* **2004**, *45*, 5505–5510.

[5] Schmidt, B.; Kunz, O. One-Flask Tethered Ring Closing Metathesis—Electrocyclic Ring Opening for the Highly Stereoselective Synthesis of Conjugated *Z/E*-Dienes. *Eur. J. Org. Chem.* **2012**, *2012*, 1008–1018.

[6] (*a*) Hoveyda, A. H.; Murphy, K. E. Enantioselective synthesis of α-alkyl-β,γ-unsaturated esters through efficient Cu-catalyzed allylic alkylations. *J. Am. Chem. Soc.* **2003**, *125*, 4690–4691; (*b*) Morin, M.D.; Rychnovsky, S. D. Reductive spiroannulation of nitriles with secondary electrophiles. *Org. Lett.* **2005**, *7*, 2051–2053; (*c*) Bartlett, P. A.; Jernstedt, K. K. A stereocontrolled synthesis of the methyl ester of (±)-nonactic acid. *Tetrahedron. Lett*. **1980**, *21*, 1607–1610; (*d*) Nicolaou, K. C.; Shi, G.-Q.; Gunzner, J. L.; Gärtner, P.; Yang, Z. Palladium-Catalyzed Functionalization of Lactones via Their Cyclic Ketene Acetal Phosphates. Efficient New Synthetic Technology for the Construction of Medium and Large Cyclic Ethers. *J. Am. Chem. Soc.* **1997**, *119*, 5467.

[7] Phosphate-containing small molecules are fundamentally important to a number of essential biological processes, including cellular transduction, lipid metabolism, and transmembrane signaling. For excellent resources on this topic, see: (a) Berridge, M. J.; Irvine, R. F. Inositol Trisphosphate, a Novel Second Messenger in Cellular Signal Transduction. *Nature* **1984**, *312*, 315–321; (b) Dzeja, P. P.; Terzic, A. Phosphotransfer Networks and Cellular Energetics. *J. Exp. Biol*. **2003**, *206*, 2039–2047; (c) Cohen, P. The Role of Protein

Phosphorylation in Neural and Hormonal Control of Cellular Activity. *Nature* **1982**, *296*, 613–620; (d) Brautbar, N.; Taberner, R-. J.; Coats, J. C.; Massry, S. G. Impaired Myocardial Lipid Metabolism in Phosphate Depletion. *Kidney Int*. **1984**, *26*, 18–23; (e) Einspahr, K. J.; Thompsom Jr., G. A. Transmembrane Signaling via Phosphatidylinositol 4,5-Bisphosphate Hydrolysis in Plants. *Plant Physiol*. **1990**, *93*, 361–366; (f) Westheimer, F. H. Why Nature Chose Phosphates. *Science* **1987**, *235*, 1173–1178; (g) Berridge M. J.; Irvine, R. F. Inositol Trisphosphate, a Novel Second Messenger in Cellular Signal Transduction. *Nature* **1984**, *312*, 315–321.

[8] For an applicable review on phosphate-containing natural products, see: Hanson, P. R.; Asad, N.; Zang, Q.; Jayasinghe, S.; Markley, J. L. 6.12. Inorganic Acid Derivatives. In *Comprehensive Organic Synthesis*, 2nd Ed., Vol. 6; Burke, S., Ed.; Elsevier Science Ltd, **2014**; pp 479–554.

[9] These FDA-approved drugs and prodrugs are examples of synthetic phosphates and include cyanocobalamin and hydroxocobalamin (synthetic forms of vitamin $B_{12}$ for treatment of vitamin $B_{12}$ deficiency), fosphenytoin (a prodrug for the treatment of epileptic seizures), amifostine (a drug used to reduce the undesired side effects of certain chemotherapy agents and radiation treatment), fludarabine (a purine analog, used as a chemotherapy drug in the treatment of B-cell chronic lymphocytic leukemia), and fosamprenavir (a prodrug of the protease inhibitor and antiretroviral drug amprenavir). These mentioned drugs and their utility can be found in DrugBank 3.0, a free online bioinformatics and cheminformatics database. For more information about DrugBank, see: (a) Knox, C.; Law, V.; Jewison, T, Liu, P.; Ly, S.; Frolkis, A.; Pon, A.; Banco, K.; Mak, C.; Neveu, V.; Djoumbou, Y.; Eisner, R.; Guo, A. C.; Wishart, D. S. DrugBank 3.0: A Comprehensive Resource for 'Omics' Research on Drugs. *Nucleic Acids Res*. **2011**, *39*, 1035–1041; (b) Wishart, D.S.; Knox, C.; Guo, A. C.; Cheng, D.; Shrivastava, S.; Tzur, D.; Gautam, B.; Hassanali, M. DrugBank: A

Knowledgebase for Drugs, Drug Actions and Drug Targets. *Nucleic Acids Res*. **2008**, *36*, 901–906; (c) Wishart, D.S.; Knox, C.; Guo, A.C.; Shrivastava, S.; Hassanali, M.; Stothard, P.; Chang, Z.; Woolsey, J. DrugBank: A Comprehensive Resource for In Silico Drug Discovery and Exploration. *Nucleic Acids Res*. **2006**, *34*, 668–672.

[10] Whitehead, A.; McReynolds, M. D.; Moore, J. D.; Hanson, P. R. Multivalent Activation in Temporary Phosphate Tethers: A New Tether for Small Molecule Synthesis. *Org. Lett.* **2005**, *7*, 3375–3378.

[11] Rychnovsky, S. D.; Griesgraber, G.; Powers, J. P. Preparation of (R,R)-1,2:4,5-Diepoxypentane [D-*threo*-Pentitol, 1,2:4,5-Dianhydro-3-deoxy-]. *Org. Synth.* **2000**, *77*, 1–11.

[12] Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. Increased Ring Closing Metathesis Activity of Ruthenium-based Olefin Metathesis Catalysts Coordinated with Imidazolin-2-ylidene Ligands. *Org. Lett.* **1999**, *1*, 953–956.

[13] In a manner similar to the naming system used in previous reports, we have generated a simplified set of identifiers that is a short-hand description of the IUPAC-designated names for each class of synthesized phosphate in order to emphasize the type of bicyclic structure formed after successful RCM. The proper names of each bicyclic phosphate are reported in the experimental section and corresponding supporting information of each manuscript. In addition, each proper name will be denoted as references throughout the chapter. In this case, bicyclo[4.3.1]phosphates refers to "2,9,10-trioxa-1-phosphabicyclo(4.3.1)dec-4-ene 1-oxides."

[14] Myers, A. G.; Zheng, B.; Movassaghi, M. Preparation of the Reagent *o*-Nitro-Benzenesulfonylhydrazide. *J. Org. Chem.* **1997**, *62*, 7507.

[15] (a) Whitehead, A.; McParland, J. P.; Hanson, P. R. Divalent Activation in Temporary Phosphate Tethers: Highly Selective Cuprate Displacement Reactions. *Org. Lett.* **2006**, *8*, 5025-5028; (b) Thomas, C. D.; McParland, J. P.; Hanson, P. R.

Divalent and Multivalent Activation in Phosphate Triesters: A Versatile Method for the Synthesis of Advanced Polyol Synthons. *Eur. J. Org. Chem.* **2009**, 5487–5500. For a recent review on general RCM that contains a section on RCM to *P*-heterocycles, see: Maitra, S.; Chegondi, R.; Markley, J. L.; Hanson, P. R. General Ring Closing Metathesis. In *Handbook of metathesis: Application in Organic Synthesis,* 2nd ed., Vol. 2; Grubbs, R. H., O'Leary, D. J., Ed.; Wiley-VCH: Weinheim, Germany, **2015**; pp 1–170.

[16] (a) Thomas, C. D. Asymmetric Synthesis of 1,3-*anti*-Diol-Containing Subunits using Phosphorus-Based Tethers: Application in the Total Synthesis of Dolabelide C. Ph.D. Thesis, University of Kansas, Lawrence, KS, November 2010; (b) Hanson, P. R.; Jayasinghe, S.; Maitra, S.; Markley, J. L. Phosphate Tethers in Natural Product Synthesis. In *Phosphorus Chemistry II,* Vol. 33, *Topis in Current Chemistry*; Montchamp, J.-L., Ed.; Springer: Switzerland, **2014**; pp 253–271.

[17] Suenaga, K.; Nagoya, T.; Shibata, T.; Kigoshi, H.; Yamada, K. Dolabelides C and D, Cytotoxic Macrolides Isolated from the Sea Hare *Dolabella auricularia.* *J. Nat. Prod.* **1997**, *60*, 155–157.

[18] Waetzig, J. D.; Hanson, P. R. A Multifaceted Phosphate Tether: Application to the C1–C14 Subunit of Dolabelides A–D. *Org. Lett*. **2008**, *10*, 109–112.

[19] Whitehead, A.; Waetzig, J. D.; Thomas, C. D.; Hanson, P. R. A Multifaceted Phosphate Tether: Application to the C15–C30 Subunit of Dolabelides A–D. *Org. Lett.* **2008**, *10*, 1421–1424.

[20] Hanson, P. R.; Chegondi, R.; Nguyen, J.; Thomas, C. D.; Waetzig, J. D.; Whitehead, A. Total Synthesis of Dolabelide C: A Phosphate-Mediated Approach. *J. Org. Chem.* **2011**, *76*, 4358–4370.

[21] Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. A Rapid Esterification by Means of Mixed Anhydride and Its Application to Large-ring Lactonization. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

[22] (a) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J., Jr.; Hoveyda, A. H. A Recyclable Ru-Based Metathesis Catalyst. *J. Am. Chem. Soc*. **1999**, *121*, 791−799; (b) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. Efficient and Recyclable Monomeric and Dendritic Ru-Based Metathesis Catalysts. *J. Am. Chem. Soc*. **2000**, *122*, 8168−8179.

[23] For a few good references on catalyst-controlled *Z*-selective metathesis processes, see: (a) Marinescu, S. C.; Levine, D. S.; Zhao, Y.; Schrock, R. R.; Hoveyda, A. H. Isolation of Pure Disubstituted *E* Olefins through Mo-Catalyzed *Z*-Selective Ethenolysis of Stereoisomeric Mixtures. *J. Am. Chem. Soc*. **2011**, *133*, 11512–11514; (*b*) Marx, V. M.; Herbert, M. B.; Keitz, B. K.; Grubbs, R. H. Stereoselective Access to *Z* and *E* Macrocycles by Ruthenium-Catalyzed *Z*-Selective Ring-Closing Metathesis and Ethenolysis. *J. Am. Chem. Soc*. **2013**, *135*, 94–97.

[24] Chegondi, R.; Tan, M. M. L.; Hanson, P. R. Phosphate Tether-Mediated Approach to the Formal Synthesis of (–)-Salicylihalamides A and B. *J. Org. Chem*. **2011**, *76*, 3909–3916.

[25] (a) Erickson, K. L.; Beutler, J. A.; Cardellina, J. H.; Boyd, M. R. Salicylihalimides A and B, Novel Cytotoxic Macrolides from the Marine Sponge *Haliclona* sp. *J. Org. Chem.* **1997**, *62*, 8188–8192. (b) Erickson, K. L.; Beutler, J. A.; Cardellina, J. H.; Boyd, M. R. Salicylihalimides A and B, Novel Cytotoxic Macrolides from the Marine Sponge *Haliclona* sp. *J. Org. Chem.* **2001**, *66*, 1532.

[26] Nicolaou, K. C.; Kim, D. W.; Baati, R. Stereocontrolled Total Synthesis of Apicularen A and Its Δ17,18-*Z*-Isomer. *Angew. Chem. Int. Ed.* **2002**, *41*, 3701–3704, and references cited therein.

[27] (a) Kridel, S. J.; Axelrod, R.; Rozenkrantz, N.; Smith J. W. Orlistat Is a novel inhibitor of fatty acid synthase with antitumor activity. *Cancer Res.* **2004**, *64*, 2070–2075; (b) Pemble, C. W.; Johnson, L. C.; Kridel, S. J.; Lowther, W. T. Crystal Structure of the Thioesterase Domain of Human Fatty Acid Synthase

Inhibited by Orlistat. *Nat. Struct. Mol. Biol.* **2007**, *14*, 704–709; (*c*) Little, J. L.; Wheeler, F. B.; Fels, D. R.; Koumenis, C.; Kridel, S. J. Inhibition of Fatty Acid Synthase Induces Endoplasmic Reticulum Stress in Tumor Cells. *Cancer Res.* **2007**, *67*, 1262–1269, and references cited therein; (d) Yang, P.-Y.; Liu, K.; Ngai, M. H.; Lear, M. J.; Wenk, M. R.; Yao, S. Q. Activity-Based Proteome Profiling of Potential Cellular Targets of Orlistat – An FDA-Approved Drug with Anti-Tumor Activities. *J. Am. Chem. Soc.* **2010**, *132*, 656–666, and references cited therein.

[28] Venukadasula, P. K. M.; Chegondi, R.; Maitra, S.; Hanson, P. R. A Concise, Phosphate-Mediated Approach to the Total Synthesis of (–)-Tetrahydrolipstatin. *Org. Lett.* **2010**, *12*, 1556–1559.

[29] Venukadasula, P. K. M.; Chegondi, R.; Suryn, G.; Hanson, P. R. A Phosphate Tether-Mediated, One-pot, Sequential Ring-Closing Metathesis/Cross-Metathesis/Chemoselective Hydrogenation Protocol. *Org. Lett.* **2012**, *14*, 2634–2637.

[30] The Pinnick oxidation was first reported by Lindgren and Nilsson, and the scope and utility later expanded by Pinnick and coworkers; see the following reference for the original work: Lindgren, B. O.; Nilsson, T. Preparation of Carboxylic Acids from Aldehydes (Including Hydroxylated Benzaldehydes) by Oxidation with Chlorite. *Acta Chem. Scand.* **1973**, *27*, 888–890.

[31] Barbier, P.; Schneider, F. Syntheses of Tetrahydrolipstatin and Absolute Configuration of Tetrahydrolipstatin and Lipstatin. *Helv. Chim. Acta.* **1987**, *70*, 196–202.

[32] (a) Juliawaty, L. D.; Kitajima, M.; Takayama, H.; Achmad, S. A.; Aimi, N. A 6-Substituted-5,6-Dihydro-2-Pyrone from *Cryptocarya strictifolia*. *Phytochemistry* **2000**, *54*, 989−993; (b) Raoelison, G. E.; Terreaux, C.; Queiroz, E. F.; Zsila, F.; Simonyi, M.; Antus, S.; Randriantsova, A.; Hostettmann, K. Absolute Configuration of Two New 6-Alkylated α-Pyrones (=2H-Pyran-2-ones) from *Ravensara crassifolia*. *Helv. Chim. Acta* **2001**, *84*, 3470−3476. (c) Jaconnet, A.;

Avelona, I.; Sahpaz, S.; Terreaux, C.; Hostettmann, K.; Stoeckli-Evans, H.; Rasolondramanitra, J. Two 6-Substituted 5,6-Dihydro-α-Pyrones from *Ravensara anisata*. *Phytochemistry* **1999**, *52*, 265−269.

[33] Jayasinghe, S.; Venukadasula, P. K. M.; Hanson, P. R. An Efficient, Modular Approach for the Synthesis of (+)-Strictifolione and a Related Natural Product. *Org. Lett.* **2014**, *16*, 122–125.

[34] (a) Chavez, D. E.; Jacobsen, E. N. Total Synthesis of Fostriecin (CI-920). *Angew. Chem. Int. Ed*. **2001**, *40*, 3667–3670; (b) Gademann, K.; Chavez, D. E.; Jacobsen, E. N. Highly Enantioselective Inverse-Electron-Demand Hetero-Diels-Alder Reactions of α,β-Unsaturated Aldehydes. *Angew. Chem. Int. Ed.* **2002**, *41*, 3059–3061; (c) Chavez, D. E.; Jacobsen, E. N.; Grabowski, E. J. J.; Kubryk, M. An Efficient, Highly Diastereo- and Enantioselective Hetero-Diels-Alder Catalyst. Preparation of (2*S*,6*R*)-6-(*tert*-Butyldimethyl-silyloxymethyl)-2-methoxy-2,5-dihydropyran. *Org. Synth.* **2005**, *82*, 34.

[35] Chegondi, R.; Hanson, P. R. Synthetic Studies To Lyngbouilloside: A Phosphate Tether-mediated Synthesis of the Macrolactone Core. *Tetrahedron Lett.* **2015**, *56*, 3330–3333.

[36] Tan, L. T.; Marquez, B. L.; Gerwick, W. H. Lyngbouilloside, a novel glycosidic macrolide from the marine cyanobacterium *Lyngbya bouillonii*. *J. Nat. Prod*. **2002**, *65*, 925–928.

[37] (a) Boeckman, R. K.; Pruitt, J. R. *J. Am. Chem. Soc.* **1989**, *111*, 8286–8288. (b) Mottet, C.; Hamelin, O.; Garavel, G.; Deprés, J.-P., Greene, A. E. *J. Org. Chem.* **1999**, *64*, 1380–1382. (c) Marshall, J. A.; Eidam, P. M. *Org. Lett.* **2008**, *10*, 93–96. (d) Reber, K. P.; Tilley, S. D.; Sorensen, E. J. *Chem. Soc. Rev.* **2009**, *38*, 3022–3034. (e) Hoye, T. R.; Danielson, M. E.; May, A. E.; Zhao, H. *J. Org. Chem.* **2010**, *75*, 7052–7060. (f) Williams, D. R.; Myers, B. J.; Mi, L.; Binder, R. J. *J. Org. Chem.* **2013**, *78*, 4762–4778.

[38] Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.

[39] Parikh, J. P.; Doering, W. E. Sulfur Trioxide in the Oxidation of Alcohols by Dimethyl Sulfoxide. *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.

[40] Brown, H. C.; Bhat, K. S. Enantiomeric *Z*- and *E*-Crotyldiisopinocampheylboranes. Synthesis in High Optical Purity of All Four Possible Stereoisomers of β-Methylhomoallyl Alcohols. *J. Am. Chem. Soc.* **1986**, *108*, 293–294.

[41] Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. Improved Procedure for the Oxidative Cleavage of Olefins by OsO4−NaIO4 *Org. Lett.* **2004**, *6*, 3217–3219.

[42] Holmquist, C. R.; Roskamp, E. J. A Selective Method For The Direct Conversion of Aldehydes Into β-Keto Esters with Ethyl Diazoacetate Catalyzed by Tin(II) Chloride. *J. Org. Chem.* **1989**, *54*, 3258–3260.

[43] Bodugam, M.; Javed, S.; Ganguly, A.; Torres, J.; Hanson, P. R. A Pot-Economical Approach to the Total Synthesis of Sch-725674. *Org. Lett.* **2016**, *18*, 516–519.

[44] Yang, S. W.; Chan, T. M.; Terracciano, J.; Loebenberg, D.; Patel, M.; Chu, M. Structure Elucidation of Sch 725674 from *Aspergillus sp*. *J. Antibiot*. **2005**, *58*, 535–538.

[45] (a) Swallen, L. C.; Boord, C. E. The Synthesis of β-Bromo-alkyl Ethers and Their Use in Further Syntheses. *J. Am. Chem. Soc.* **1930**, *52*, 651–660; (b) Shoemaker, B. H.; Boord, C. E. Nuclear Syntheses in the Olefin Series. II. 1,4-Diolefins. *J. Am. Chem. Soc.* **1931**, *53*, 1505–1512.

[46] Bali, A. K.; Sunnam, S. K.; Prasad, K. R. Enantiospecific Total Synthesis of Macrolactone Sch 725674. *Org. Lett.* **2014**, *16*, 4001–4008.

[47] Hanson, P. R.; Jayasinghe, S.; Maitra, S.; Ndi, C. N.; Chegondi, R. A Modular Phosphate Tether-mediated Divergent Strategy to Complex Polyols. *Beilstein J. Org. Chem.* **2014**, *10*, 2332–2337.

[48] Javed, S.; Bodugam, M.; Torres, J.; Ganguly, A.; Hanson, P. R. Modular Synthesis of Novel Macrocycles Bearing α,β-Unsaturated Chemotypes via a Series of One-Pot, Sequential Protocols. *Chem. Eur. J.* **2016**, *22*, 6755–6758.

[49] Phosphonylation was carried out over 2 pots. See Ref 48.

[50] Maitra, S.; Bodugam, M.; Javed, S. Synthesis of the C9–C25 Subunit of Spirastrellolide B. *Org. Lett.* **2016**, ASAP.

[51] Warabi, K.; Williams, D. E.; Patrick, B. O.; Roberge, M.; Andersen, R. J. Spirastrellolide B Reveals the Absolute Configuration of the Spirastrellolide Macrolide Core. *J. Am. Chem. Soc.* **2007**, *129*, 508–509.

[52] This strategy is comparable to that utilized by Deshong and Tong to generate the key spiroketal moiety of a similar intermediate. (a) Harris, J. M.; Li, M.; Scott, J. G.; O'Doherty, G. A. Achmatowicz Approach to 5,6-Dihydro-2H-pyran-2-one Containing Natural Products. In *Strategies and Tactics in Organic Synthesis*; Harmata, M., Ed.; Elsevier: 2004; Vol. 5, pp 221–253. For similar strategies, see: (b) Zhu, L.; Song, L.; Tong, R. Diastereoselective Reductive Ring Expansion of Spiroketal Dihydropyranones to *cis*-Fused Bicyclic Ethers. *Org. Lett*. **2012**, *14*, 5892–5895; (c) Perron, F.; Albizati, K. F. Synthesis of Oxidized Spiroketals via 2-Furyl Ketone Oxidation-Rearrangement. *J. Org. Chem*. **1989**, *54*, 2044–2047; (d) DeShong, P.; Waltermire, R. E.; Ammon, H. L. A General Approach to the Stereoselective Synthesis of Spiroketals: A Total Synthesis of the Pheromones of the Olive Fruit Fly and Related Compounds. *J. Am. Chem. Soc*. **1988**, *110*, 1901–1910. For different applications, see: (e) Burke, M. D.; Berger, E. M.; Schreiber, S. L. A Synthesis Strategy Yielding Skeletally Diverse Small Molecules Combinatorially. *J. Am. Chem. Soc.* **2004**, *126*, 14095–14104; (f) Herrmann, A. T.; Martinez, S. R.; Zakarian, A. A Concise Asymmetric Total Synthesis of (+)-

Brevisamide. *Org. Lett.* **2011**, *13*, 3636–3639; (g) Leverett, C. A.; Cassidy, M. P.; Padwa, A. Application of the Aza-Achmatowicz Oxidative Rearrangement for the Stereoselective Synthesis of the Cassia and Prosopis Alkaloid Family. *J. Org. Chem.* **2006**, *71*, 8591–8601; (h) DeShong, P.; Ramesh, S.; Elango, V.; Perez, J. J. Total Synthesis of (±)-Tirandamycin A. *J. Am. Chem. Soc.* **1985**, *107*, 5219–5224; (i) Nicolaou, K. C.; Baker, T. M.; Nakamura, T. Synthesis of the WXYZA′ Domain of Maitotoxin. *J. Am. Chem. Soc.* **2011**, *133*, 220–226; (j) Henderson, J. A.; Jackson, K. L.; Phillips, A. J. Highly Functionalized Pyranopyrans from Furans: A Synthesis of the C27−C38 and C44−C53 Subunits of Norhalichondrin B. *Org. Lett*. **2007**, *9*, 5299–5302; (k) Snider, B. B.; Wu, X.; Nakamura, S.; Hashimoto, S. A Short, Formal, Biomimetic Synthesis of (±)-Polygalolides A and B. *Org. Lett*. **2007**, *9*, 873–874; (l) Zhang, W.; Tong, R. Synthetic Approaches To Construct the 6,8-DOBCO Framework in Natural Products. *J. Org. Chem*. **2016**, *81*, 2203–2212, and references within.

[53] Mulzer, J.; Berger, M. Total Synthesis of the Boron-Containing Ion Carrier Antibiotic Macrodiolide Tartrolon B. *J. Org. Chem.* **2004**, *69*, 891–898.

[54] (a) Corey, E. J.; Helal, C. J. Reduction of Carbonyl Compounds with Chiral Oxazaborolidine Catalysts: A New Paradigm for Enantioselective Catalysis and a Powerful New Synthetic Method. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012; (b) Kumar, V. P.; Chandrasekhar, S. Enantioselective Synthesis of Pladienolide B and Truncated Analogues as New Anticancer Agents. *Org. Lett.* **2013**, *15*, 3610–3613.

[55] (a) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroeder, G.; Sharpless, K. B. Asymmetric dihydroxylation via ligand-accelerated catalysis. *J. Am. Chem. Soc*. **1988**, *110*, 1968–1970; (b) Keaton, K. A.; Phillips, A. J. Toward the Synthesis of Spirastrellolide B: a Synthesis of the C1–C23 Subunit. *Org. Lett.* **2008**, *10*, 1083–1086.

# Chapter 2

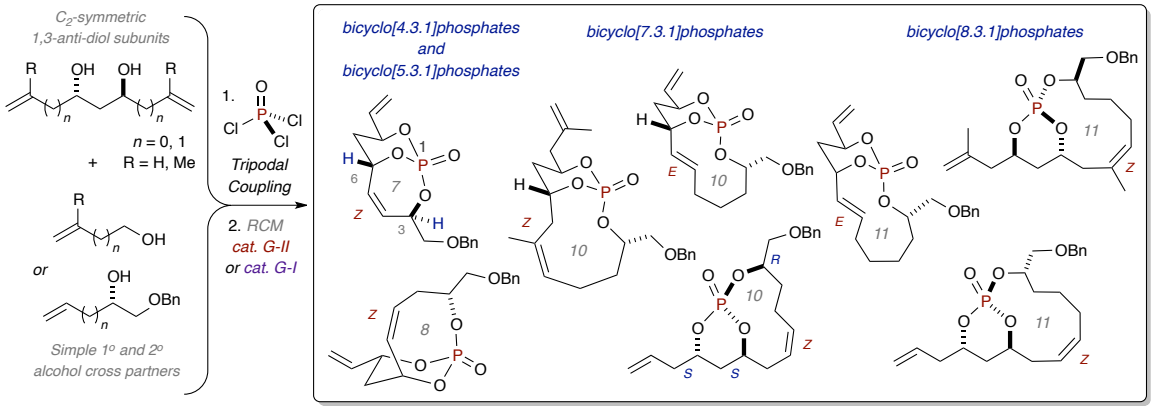
*Phosphate Tether-Mediated Ring-Closing Metathesis Studies to Bicyclo[n.3.1]phosphates: Extended Investigations on the Effect of Ring Size, Stereochemical Complexity, and Olefin Substitution*

## 2.1 Introduction

The development of methods that allow for the mild, high-yielding, and predictable coupling of simple chemical fragments to provide complex intermediates from core motifs common to a variety of natural products stands at the forefront of modern-day organic synthesis. In particular, methods that employ temporary tether strategies have emerged as intriguing tools to control substrate reactivity, site specificity and stereochemical outcome of tether-mediated transformations.[1] While the use and study of temporary silicon-based tether systems in RCM is well represented in the literature,[2] on-going efforts in our group have sought to exploit the inherent properties of phosphate triesters to develop tripodal *P*-tether systems[3] for the generation of complex polyol-containing intermediates en route to the total synthesis of natural products (see Chapter 1 of this thesis). This work has led to the completion of a number of total and formal syntheses, including dolabelide C,[4] salicylihalimide A (formal synthesis),[5] (–)-tetrahydrolipstatin,[6] (+)-strictifolione,[7] and lyngbouilloside (core macrolactone).[8] In an effort to expand the scope of the method, in 2013, we completed a detailed study on the effects of ring size and stereochemical complexity on the successful formation of bicyclo[4.3.1]-,[9] bicyclo[5.3.1]-,[10] and bicyclo[7.3.1]phosphates[11,12] via diastereoselective RCM.[13] In 2015, we published a continuation of these efforts to provide a number of stereochemically complex bicyclo[6.3.1]phosphates,[14] along with a few simple examples of bicyclo[7.3.1]- and bicyclo[8.3.1]phosphates.[15,16] However, the complexity of large ring dynamics—combined with the small sample size of bicyclo[7.3.1]- and bicyclo[8.3.1]phosphates in both studies—can complicate the generalization of those

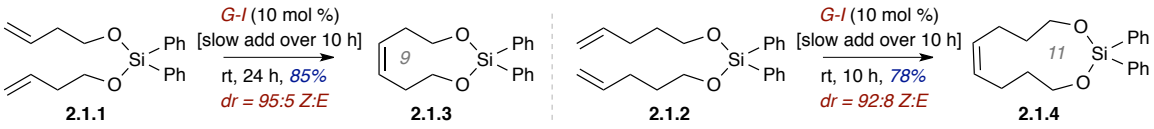
findings. Since the preliminary studies represented some of the first reports of RCM to afford phosphates of this ring size, much still remains to be discovered in this particular area of macrocyclic phosphate synthesis. Thus, in 2016, we reported an investigation that expands upon previous efforts by focusing on the formation of bicyclo[7.3.1]- and bicyclo[8.3.1]phosphates (10- and 11-membered RCM), with a special emphasis on the effect of olefin- and C3-substition, as well as proximity of the forming olefin to the bridgehead carbon of the resultant bicyclic phosphate, on the success and stereochemical outcome of the macrocyclic, ring-closing metathesis event.[17] This chapter presents our recent work in *P*-tether-mediated RCM studies to provide a variety of *P*-stereogenic bicyclo[4.3.1]-, bicyclo[5.3.1]-, bicyclo[7.3.1]-, and bicyclo[8.3.1]phosphates, with a detailed analysis of the factors affecting 10- and 11-membered ring formation (Figure 2.1).

**Figure 2.1**. *Ring-closing metathesis to medium- and large-ring containing bicyclo[n.3.1]phosphates.*



*2.1.1 Temporary Silicon Tethered Ring-Closing Metathesis in the Formation of Medium to Large Rings*

Though the vast majority of temporary silicon tether-mediated ring-closing metatheses (TST-RCM) result in the formation 7- or 8-membered rings,[2] investigations involving the generation of medium- to large-ring-containing silicon heterocycles via RCM have been reported—albeit in limited scope. In 1999, Hoye and Promo reported a study focused on TST-RCM reactions for self- and cross-coupling of alkenyl alcohols.[18] Investigations included the formation of 7-, 9-, and 11-membered silicon heterocycles, and a few examples are shown in Scheme 2.1. Dienes **2.1.1** and **2.1.2**, derived from the coupling of diphenylchlorosilane with the appropriate olefinic alcohol, were treated with Grubbs first generation catalyst[19] (G-I, 10 mol %, added slowly over 10 hours) to provide the corresponding 9- and 11-membered monocyclic silicon heterocycles in good yield and high *Z*-selectivity (Scheme 2.1). The authors noted, that although the formation of *Z*-configured olefins was overwhelmingly preferred, small amounts of stereoisomer (assigned as the *E*-diastereomer) were observed by GC and GC-MS for nearly every example, and unsurprisingly, selectivity tended to decrease with increasing ring-size.

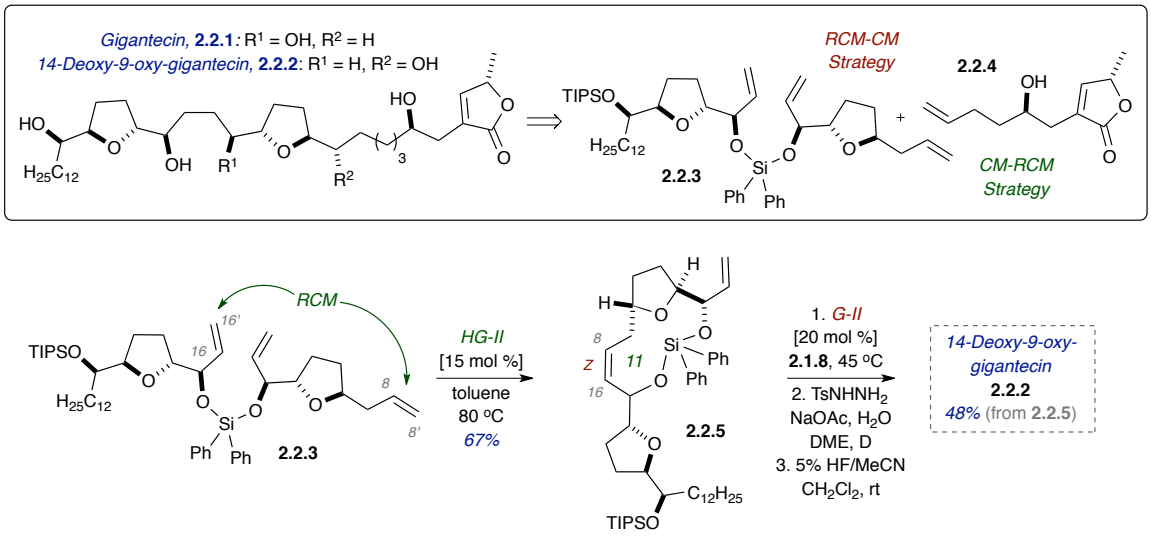



**2.1.1** **2.1.3** **2.1.2** **2.1.4**

**Scheme 2.1** *Temporary silicon-tether mediated RCM to 9- and 11-membered silicycles.*

In 2006, the same group reported the use of temporary silicon tether-mediated RCM en route to the total synthesis of cytotoxic, anti-tumor agent (+)-gigantecin (**2.2.1**) and 14-deoxy-9-oxy-gigantecin (**2.2.2**) (Scheme 2.2).[20] The authors proposed that **2.2.1**

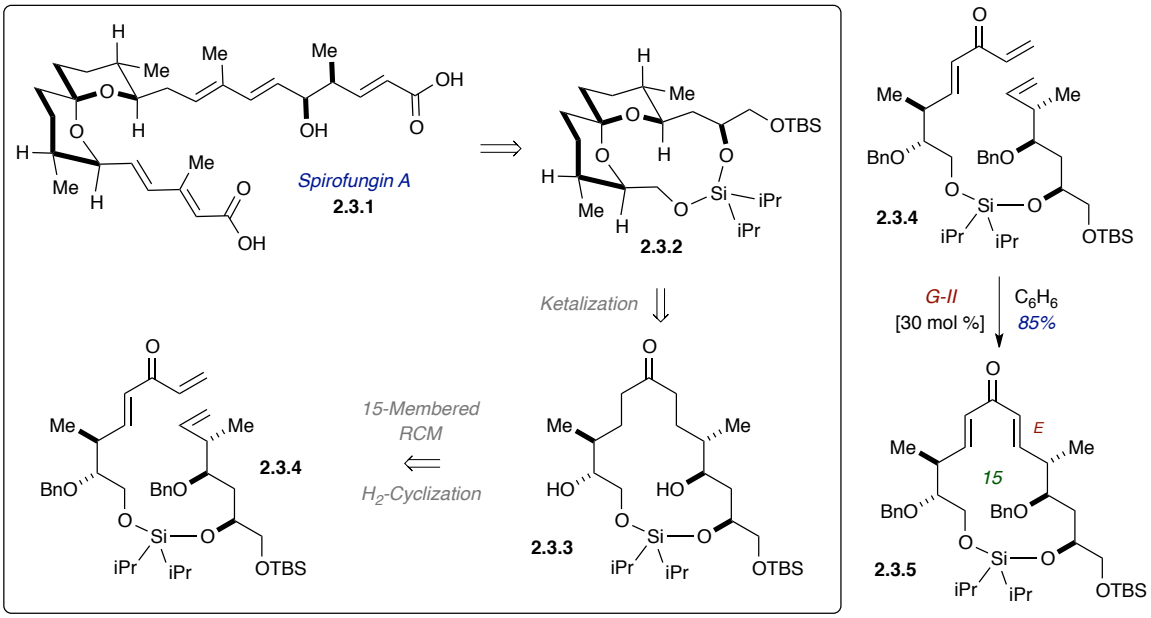
could be derived from triene **2.2.3** and lactone **2.2.4** via a one-pot, three-component RCM-CM or CM-RCM metathesis strategy involving the formation of an intermediate 7-membered ring-containing silicon heterocycle. However, treatment of triene **2.2.3** with Hoveyda-Grubbs second-generation catalyst[21] (HG-II, 15 mol %), in refluxing toluene, provided 11-membered ring-containing **2.2.5**, instead of the expected 7-membered ring. The authors hypothesize that the formation of **2.2.5** is the direct result of preferential catalyst-initiation at the more active, Type I-like C8-olefin. Cross-metathesis of **2.2.5** with **2.2.4**, in the presence of Grubbs second-generation catalyst[22] (G-II, $[(ImesH_2)(PCy_3)(Cl)_2Ru{=}CHPh]$, 20 mol %), followed by diimide reduction and global silicon-deprotection, then afforded 14-deoxy-9-oxy-gigantecin, **2.2.2**, in 48% yield.




**Scheme 2.2** *Temporary silicon-tether mediated RCM to 9- and 11-membered silicycles en route to the total synthesis of gigantecin.*

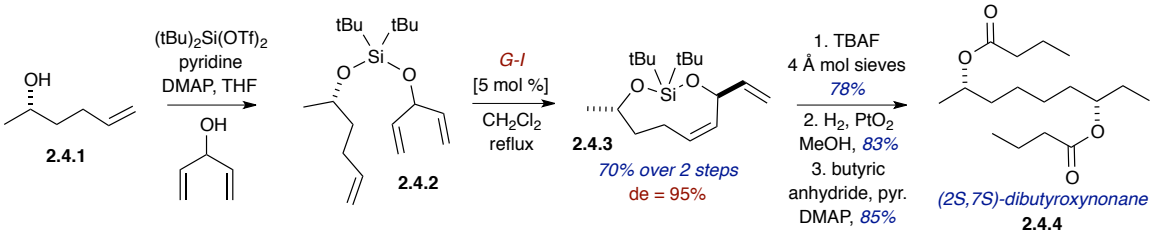
In 2007, Kozmin and Marjanovic published the stereoselective synthesis of anti-proliferative natural product spirofungin A (**2.3.1**) via the use of a 15-membered, *E*-

selective silicon-tethered RCM reaction (Scheme 2.3).[23] Retrosynthetic analysis of spirofungin A (**2.3.1**) revealed that the natural product could be formed via silicon-containing spiroketal-core **2.3.2**, which results from a silicon-tether-mediated ketalizaiton of diol-containing, macrocyclic ketone **2.3.3**. In turn, **2.3.3** could be provided via a Si-tether-mediated 15-membered RCM of **2.3.4**, followed by a hydrogenation/deprotection/ketalization protocol. As predicted, treatment of **2.3.4** with G-II (20 mol %), in refluxing benzene, generated the corresponding *E*-configured, 15-membered, monocyclic silicon heterocycle **2.3.5** in 85% yield. The authors highlight that this RCM proceeded chemoselectively between the two terminal olefins of **2.3.4**, and none of the truncated 12-membered RCM product was observed.




**Scheme 2.3** *Temporary silicon-tether mediated RCM to 15-membered silicycle* ***2.3.5*** *en route to the total synthesis of spirofungin A.*

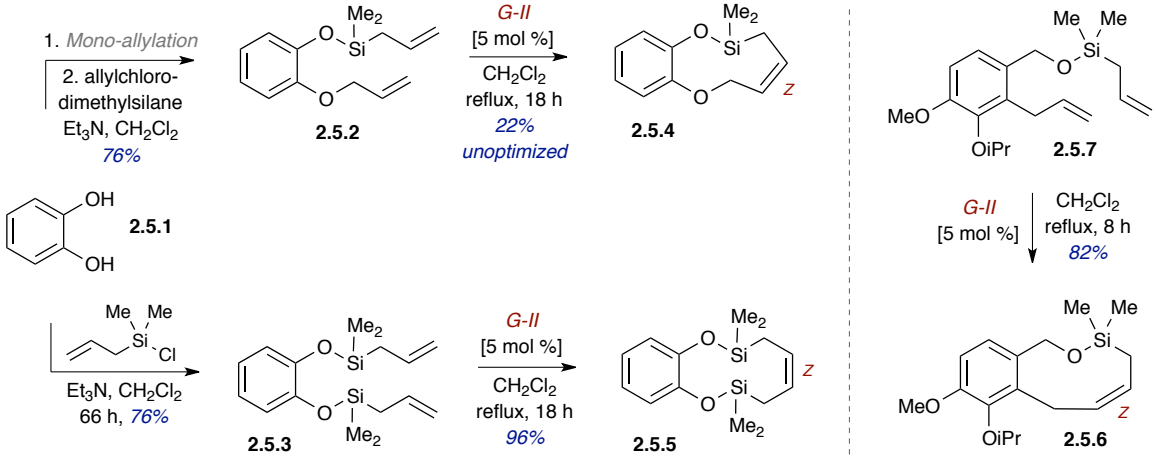
In 2007, Pickett and coworkers reported the use of diastereoselective silicon-tethered RCM en route to the synthesis of (2*S*,7*S*)-dibutyroxynonane (**2.4.4**), a sex pheromone of the orange wheat blossom midge *Sitodiplosis mosellana* used to optimize pesticide treatment of wheat (Scheme 2.4).[24] Chiral, non-racemic olefinic alcohol **2.4.1** was coupled with pro-chiral 1,4-pentadien-3-ol, in the presence of di-*tert*-butylsilyltriflate, pyridine, and facilitating 4-dimethylaminopyridine, to provide silylketal **2.4.2**, which was filtered through a neutral aluminum plug and concentrated. Subsequent RCM with G-I (5 mol %), in refluxing methylene chloride, generated 9-membered silicon heterocycle **2.4.3** in 70% yield over 2 steps, 95% diastereomeric excess, and high *Z*-selectivity. Silyl-deprotection with TBAF, global hydrogenation with $H_2/PtO_2$, and acylation with butyric anhydride then provided (2*S*,7*S*)-dibutyroxynonane (**2.4.4**) in good overall yield.




**Scheme 2.4** *Silicon-tether mediated RCM to 9-membered silicycle en route to the synthesis of (2S,7S)-dibutyroxynonane.*

In 2008, van Otterlo and coworkers published an RCM strategy for the synthesis of novel 9- and 10-membered silicon-containing benzo-fuzed heterocycles derived from catechol starting materials—a select few are shown in Scheme 2.5.[25] Catechol (**2.5.1**) was functionalized [mono-allylation, followed by treatment with allylchlorosilane or di-

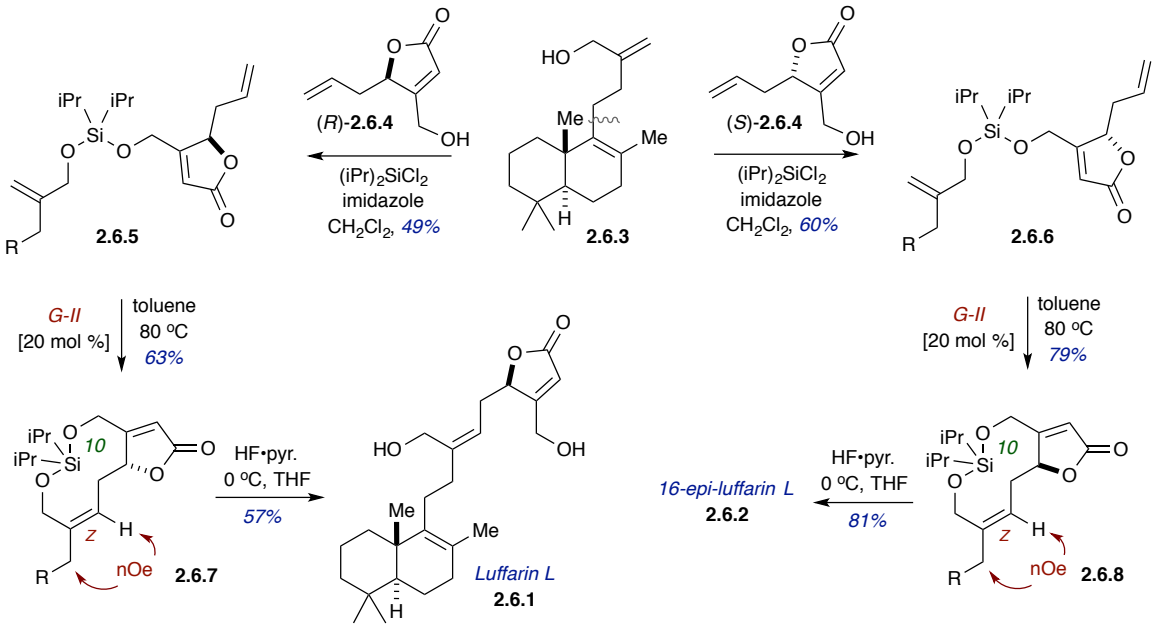
silylation via treatment with excess allylchlorosilane] to provide phenoxysilanes **2.5.2** and **2.5.3** in good overall yield. Subsequent treatment of **2.5.2** with G-II (5 mol %) in refluxing methylene chloride provided *Z*-configured, 9-membered silicon heterocycle **2.5.4**, albeit in low unoptimized yield. Similarly, RCM of phenoxysilane **2.5.3** under similar reaction conditions afforded *Z*-configured, 10-membered silicon heterocycle **2.5.5** in 96% yield. An analogous 9-membered benzofused silicon heterocycle, **2.5.6**, was generated in 82% yield from the corresponding diene **2.5.7**—proving that high-yielding 9-membered ring formation of benzo-fused silicon heterocycles of this type is also achievable via RCM.




**Scheme 2.5** *Silicon-tether mediated RCM to 9- and 10-membered silicycles.*

Recently, in 2015, Basabe and coworkers reported the synthesis of anti-proliferative natural products luffarin L (**2.6.1**) and 16-epi-luffarin L (**2.6.2**) via a temporary silicon tether-mediated RCM protocol and the formation of intermediate 10-membered-ring containing monocyclic silaketals (Scheme 2.6). In this regard, commercially available (–)-sclareol (**2.6.3**) was coupled with (*R*)-**2.6.4** or (*S*)-**2.6.4**, in the

presence of diisopropylchlorosilane and imidazole, to provide diastereomeric silaketals **2.6.5** and **2.6.6** in 49% and 60% yields, respectively. Subsequent RCM with G-II (20 mol %), carried out in toluene at 80 °C, furnished *Z*-configured, 10-membered silicon heterocycles **2.6.7** and **2.6.8** in moderate to good yield, and olefin configuration was confirmed by NOE $^{1}$H NMR analysis. Finally, silyl-deprotection with HF•pyridine afforded luffarin L (**2.6.1**) and 16-*epi*-luffarin L (**2.6.2**) in 57% and 81% yields, respectively.



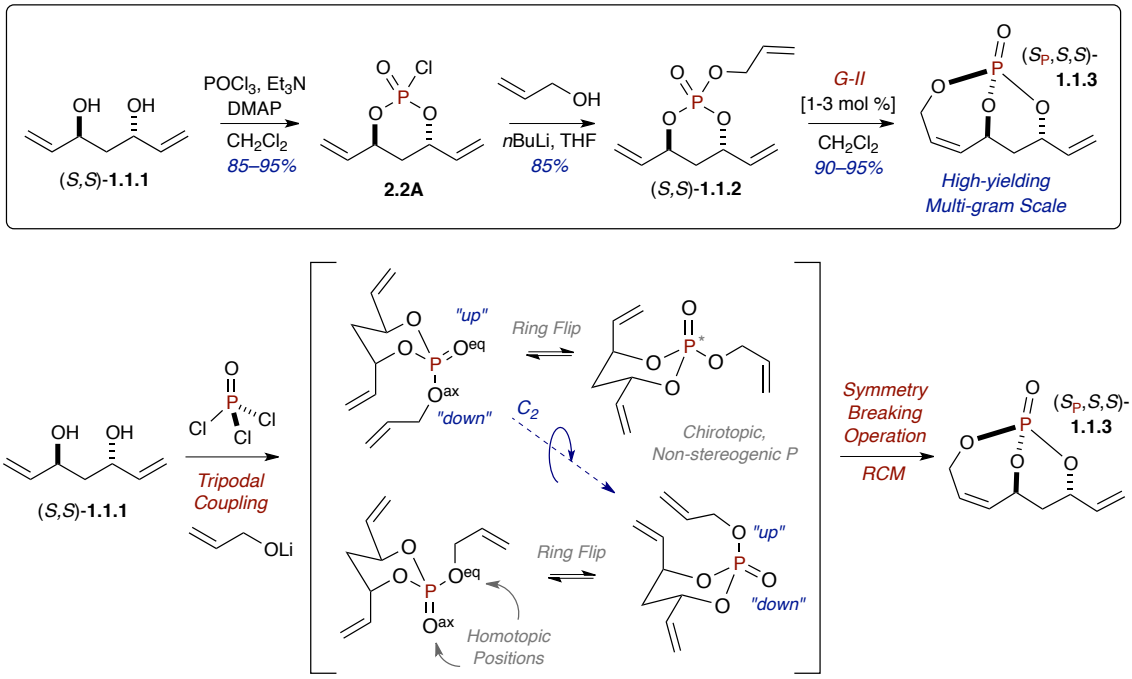

**Scheme 2.6** *Temporary silicon tether-mediated RCM to 10-membered silicon heterocycles en route to the synthesis of luffarin L.*

*2.1.2 Phosphate Tether-Mediated Ring-Closing Metathesis for the Synthesis of P-Stereogenic Bicyclo[4.3.1]phosphates: Conformational Analysis and Rationalization of Diastereoselectivity*

In 2005, our group reported the desymmetrization of $C_2$-symmetric, 1,3-*anti*-diol-containing dienes through a phosphate tether-mediated diastereoselective ring-closing olefin metathesis reaction (Figure 2.2).[3] As previously described (see Chapter 1 of this thesis), dienediol (*S,S*)-**1.1.1**[26]—or the corresponding enantiomer—could be coupled with $POCl_3$, in the presence of triethylamine and catalytic 4-dimethylaminopyridine (DMAP), to provide a relatively unstable intermediate monochlorophosphate (**2.2A**) in excellent yields. This intermediate was then immediately coupled with the lithium alkoxide of allyl alcohol to afford phosphate triene (*S,S*)-**1.1.2**. As shown in Figure 2.2, this pseudo-$C_2$-symmetric triene, which possesses a chirotopic, non-stereogenic phosphorus atom, can exist in either of two possible conformations—the four conformations shown reduce to two autonomous conformations by nature of a central $C_2$-axis of symmetry that bisects the molecule. Treatment of triene (*S,S*)-**1.1.2** with Grubbs second generation catalyst [$(ImesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$][27] or Hoveyda-Grubbs second generation catalyst[28] results in a symmetry-breaking ring-closing metathesis (RCM) reaction and furnishes a single diastereomer of bicyclic phosphate—in this case, ($S_P$,*S,S*)-**1.1.3**. The reactivity profile of this bicyclic phosphate, and its corresponding enantiomer, were detailed in a number of investigations—most of which focused on the functionalization of the exocyclic olefin and $S_N2$'-cuprate additions to the endocyclic olefin.[3,29] However, few studies had been undertaken to detail the effects of stereochemical complexity, ring-size,

and olefin substitution on the success and stereochemical outcome of the *P*-tether mediated, diastereoselective ring-closing metathesis event. Thus, efforts were focused on the generation of a variety of diverse model systems to provide a better understanding of these factors in an effort to expand the scope of the method and its applicability in the coupling of both simple and complex chemical fragments en route to the total synthesis of natural products and biologically active small molecules.

**Figure 2.2** *Synthesis of simple bicyclo[4.3.1]phosphates and conformational rationale for diastereoselectivity.*

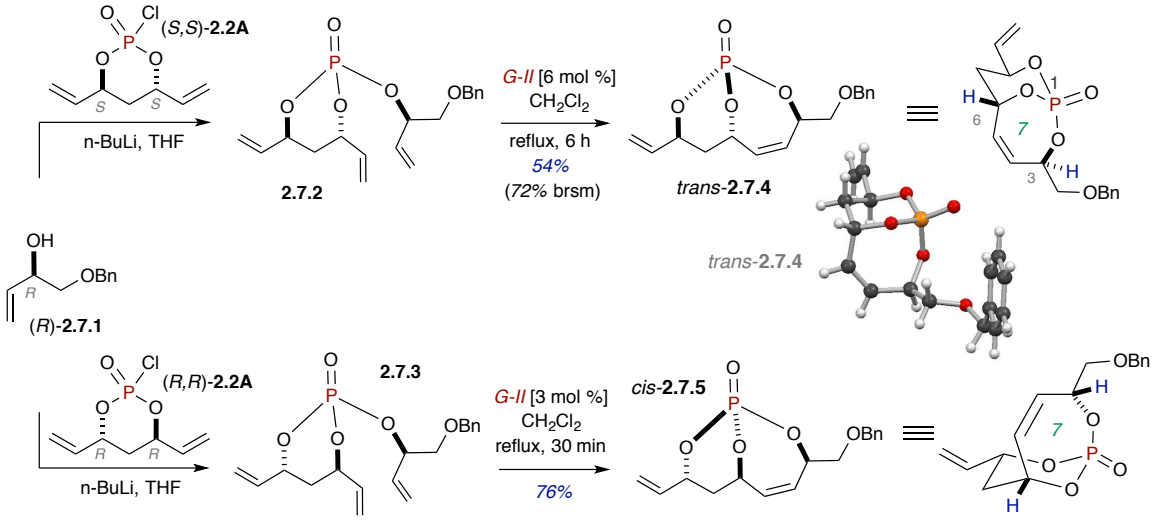



## 2.2 Results and Discussion

### *2.2.1 Syntheiss of Bicyclo[4.3.1]-, Bicyclo[5.3.1]-, and Bicyclo[6.3.1]phosphates*

We first investigated the effect of C3-substitution on the formation of bicyclo[4.3.1]phosphates via 7-membered ring-forming RCM.[12] To this end, chiral, non-

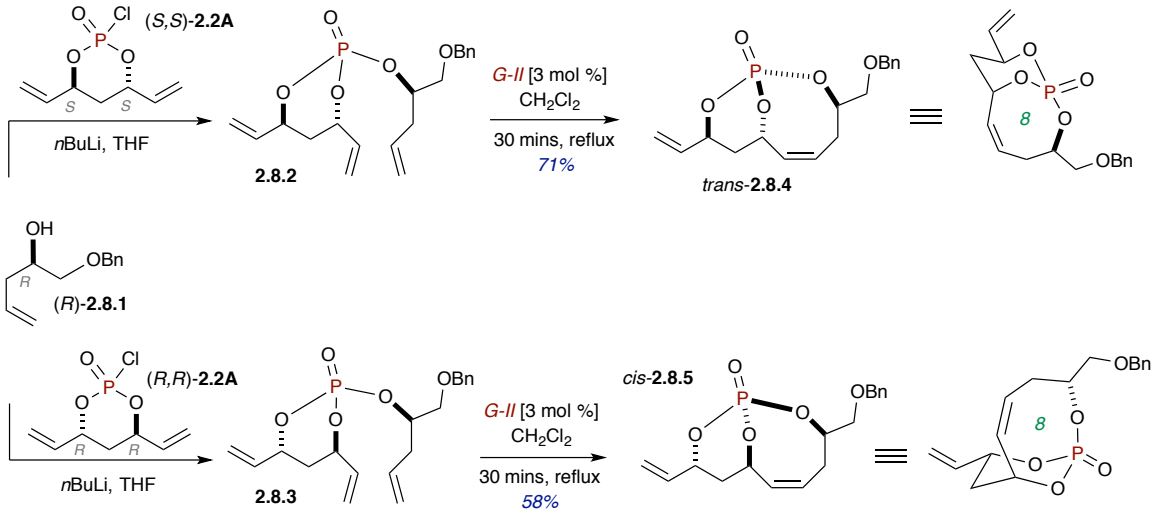
racemic allylic alcohol **2.7.1**[30] was coupled with enantiomeric monochlorophosphates (*S,S*)-**2.2A** and (*R,R*)-**2.2A** to generate diastereomeric trienes **2.7.2** and **2.7.3**, respectively (Scheme 2.7).[31] Trienes **2.7.2** and **2.7.3** were exposed to G-II (6 mol % and 3 mol %, respectively) to provide the corresponding bicyclo[4.3.1]phosphates *trans*-**2.7.4** and *cis*-**2.7.5**[32] in 54% and 76% yields, respectively (similar yields based on recovered starting material). X-ray crystallographic analysis revealed the caged conformation of *trans*-**2.7.4** where the C3-substitutent (-$CH_2$OBn) points toward the concave face of the bicyclic phosphate;[33] it was proposed that the orientation of this C3-substituent results in steric strain which manifests in the requirement of higher catalyst loadings and extended reaction times to provide *trans*-**2.7.4** versus *cis*-**2.7.5**.




**Scheme 2.7** *Synthesis of 3-substituted bicyclo[4.3.1]phosphates.*

In addition to bicyclo[4.3.1]phosphate formation, the effect of C3-substitution on the generation of bicyclo[5.3.1]phosphates via 8-membered ring-forming RCM was studied.[12] Thus, chiral, non-racemic homoallylic alcohol **2.8.1**[34] was coupled with enantiomeric monochlorophosphates (*S,S*)-**2.2A** and (*R,R*)-**2.2A** to provide

diastereomeric trienes **2.8.2** and **2.8.3**, which were treated with G-II catalyst to afford the corresponding bicyclo[5.3.1]phosphates *trans*-**2.8.4** and *cis*-**2.8.5** in 71% and 58% yields, respectively (Scheme 2.8). Notably, the generation of bicyclo[5.3.1]phosphates *cis*-**2.8.5** and *trans*-**2.8.4** proceeded under similar reaction conditions (catalyst loading and reaction times), unlike the analogous bicyclo[4.3.1]phosphate examples.

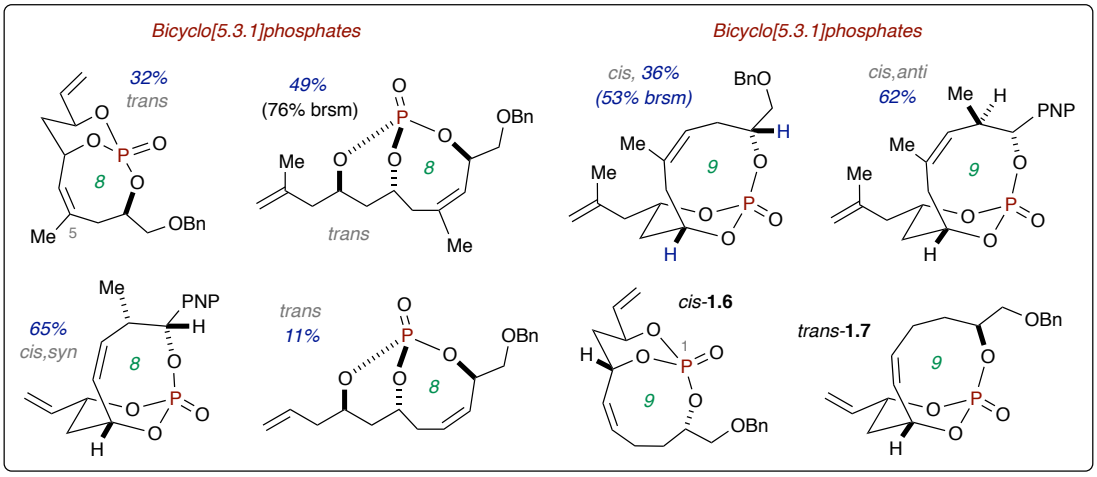



**Scheme 2.8** *Synthesis of 3-substituted bicyclo[5.3.1]phosphates.*

Following similar protocols, a variety of stereochemically rich bicyclo[5.3.1]- and bicyclo[6.3.1]phosphates, with and without olefin substitution, were synthesized via phosphate tether-mediated RCM (Figure 2.3).[12,16,35] In the case of the bicyclo[5.3.1]- and bicyclo[6.3.1]phosphate formation, a mechanistic rationale for the observed reactivity based upon proposed Ru-metallocyclobutane intermediate structures was developed, highlighting the similarities and differences for observed reactivity of bicyclo[6.3.1]phosphates to their smaller bicyclo[5.3.1]phosphate counterparts. As the formation of these stereochemically rich, 8- and 9-membered ring-containing bicyclic phosphates has been previously reported in another thesis,[35] only a select few of the

examples which resulted in successful formation of the bicyclic phosphate are shown in Figure 2.3, and a detailed review of this portion of the study will not be described here.

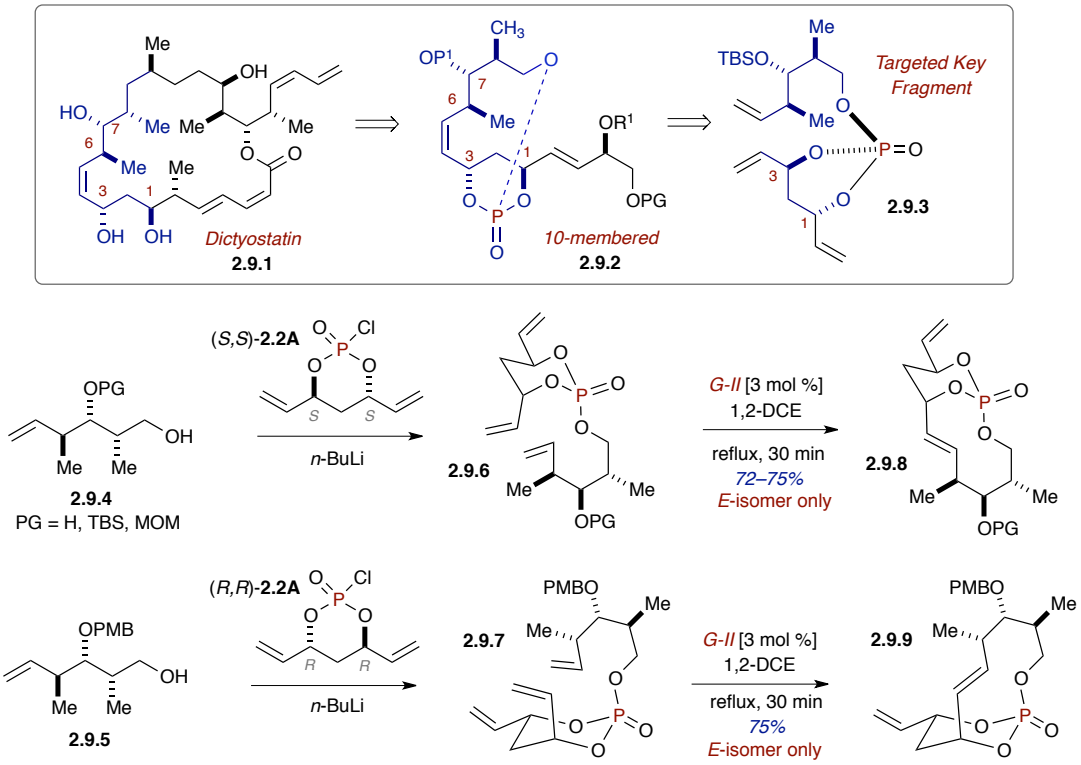
**Figure 2.3** *Other stereochemically rich bicyclo[5.3.1]- and bicyclo[6.3.1]phosphates generated via phosphate tether-mediated RCM.*




*2.2.2 Synthesis of Bicyclo[7.3.1]phosphates*

In addition to the synthesis of a number of bicyclo[4.3.1]- and bicyclo[5.3.1]phosphates, the formation of stereochemically rich bicyclo[7.3.1]-phosphates was also explored, in pursuit of the total synthesis of dictyostatin (**2.9.1**) (Scheme 2.9).[12,35,36] Retrosynthetic analysis of the natural product revealed that it could be formed via 10-membered ring-containing bicyclic phosphate **2.9.2**, which could be accessed via a *Z*-selective ring-closing metathesis of the corresponding triene (**2.9.3**). To test the viability of this strategy, we coupled dictyostatin-like cross-partners **2.9.4** and **2.9.5**[37] with monochlorophosphates (*S,S*)-**2.2A** and (*R,R*)-**2.2A** to generate diastereomeric phosphate trienes **2.9.6** and **2.9.7**. Subsequent RCM with G-II, in refluxing 1,2-dichloroethane, afforded bicyclo[7.3.1]phosphates **2.9.8** and **2.9.9** in good yield and high

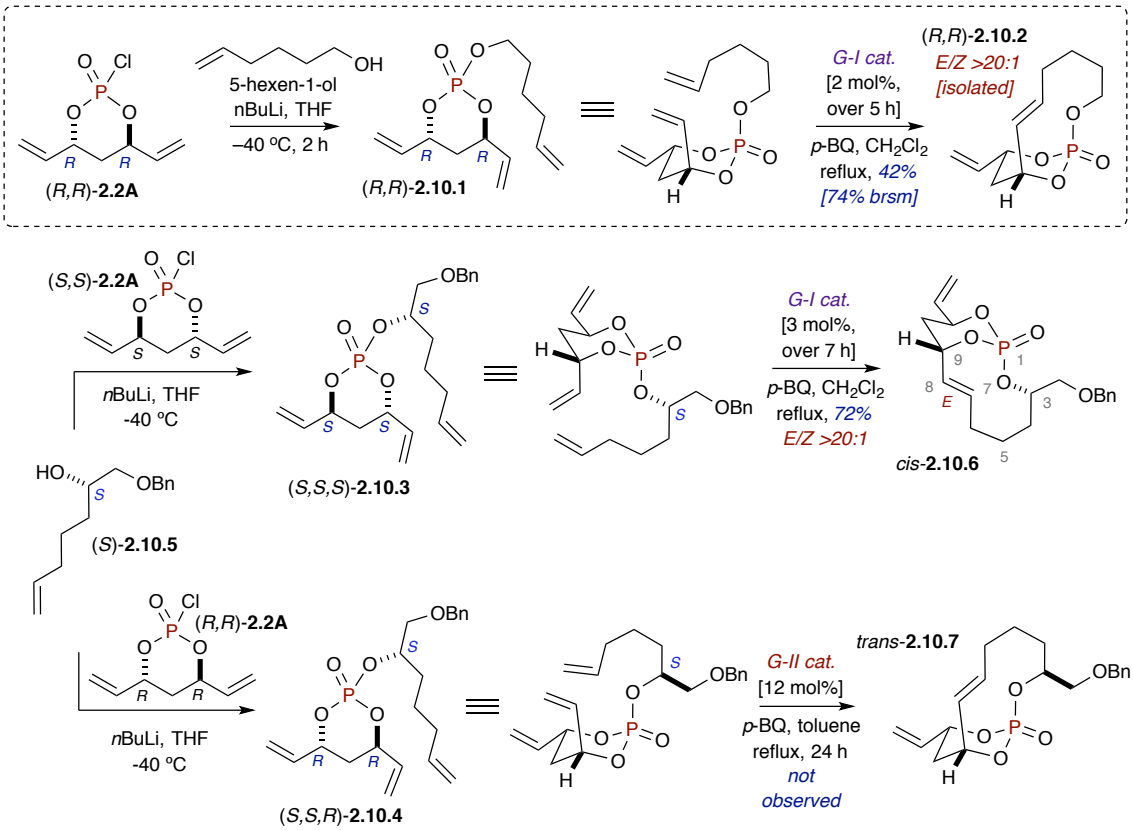
*E*-selectivity (dr > 20:1). Because studies of monocyclic silicon-tether systems have shown that stereochemical complexity of tether fragments can influence the stereoselectivity of temporary silicon tether-mediated RCM,[2d] we proposed that the stereochemistry in the side-chain of phosphates **2.9.8** and **2.9.9** could have a similar impact on the stereoselectivity of the *P*-tether-mediated RCM event.




**Scheme 2.9** *Synthetic efforts toward dictyostatin and the synthesis of stereochemically rich bicyclo[7.3.1]phosphates.*

Thus, a series of simplified phosphate triester trienes were designed to assess the impact of stereochemical complexity on the stereoselectivity of phosphate tether-mediated RCM in bicyclo[7.3.1]phosphate formation. Coupling of (*R,R*)-monochlorophosphate **2.2A** with the lithium alkoxide of 5-hexen-1-ol provided

phosphate triene (*R,R*)-**2.10.1**, which was treated with Grubbs first generation catalyst (G-I)[38] to furnish bicyclo[7.3.1]phosphate **2.10.2** in 42% yield (74% yield based on recovered starting material) and, again, high *E*-selectivity (Scheme 2.10). This implied that ring size—and not stereochemical complexity—may be the most influential factor in the stereoselectivity of RCM to form bicyclo[7.3.1]phosphates, as it may contribute to flexibility in large-ring dynamics that allows the more stable *trans*-configured olefin to be energetically feasible (and thermodynamically favorable).



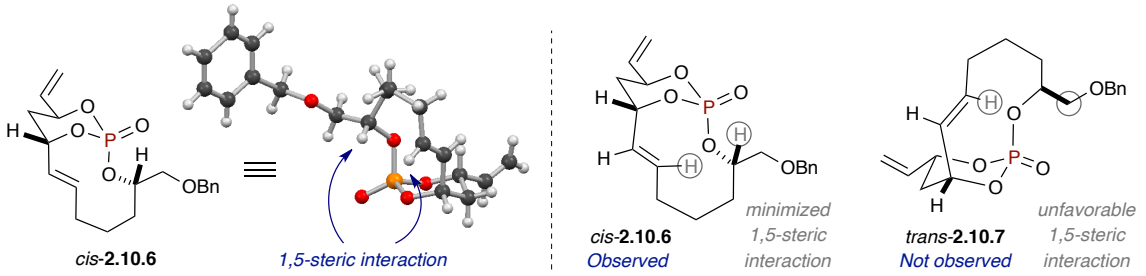

**Scheme 2.10** *The synthesis of simplified bicyclo[7.3.1]phosphates and the effect of C3-substitution on the successful formation of bicyclic phosphate.*

The effect of C3-substitution on *P*-tether mediated RCM was next explored, and trienes (*S,S,S*)-**2.10.3** and (*R,R,S*)-**2.10.4** were generated via the coupling of olefinic alcohol (*S*)-**2.10.5**[39] with monochlorophosphates (*S,S*)-**2.2A** and (*R,R*)-**2.2A** (Scheme 2.10). Triene (*S,S,S*)-**2.10.3** was exposed to G-I catalyst (3 mol %, slow addition), in refluxing methylene chloride, to provide *cis*-**2.10.6** in 72% yield and high *E*-selectivity. However, attempts at the RCM of triene (*R,R,S*)-**2.10.4** to form *trans*-**2.10.7** were unsuccessful, even under forcing conditions. This result was surprising, as the stereochemical complexity of trienes **2.9.6** and **2.9.7** did not inhibit the formation of the corresponding bicyclo[7.3.1]phosphates (see above, Scheme 2.9).

Due to the complexity of large ring dynamics—which was further complicated by the possibility of forming either *E*- or *Z*-configured olefins within large rings, it is difficult to develop a mechanistic rationale derived from proposed structures for intermediate Ru-metallocyclobutanes. However, X-ray crystallographic analysis of *cis*-**2.10.6**[40] showed a 1,5-steric interaction between the C–H bond of the endocyclic olefin (C7) and the C–H bond of the C3-position (Figure 2.4). Thus, based solely on the conformations of the product, a pronounced 1,5-steric interaction between the substituents on the endocyclic olefin and the C3-position of the olefin tether-partner could be responsible for the observed reactivity. When the β-C3-substituent of the olefinic tether-partner is hydrogen, the reaction proceeds—presumably because this 1,5-interaction is minimized when both interacting groups are hydrogen; however, when the β-substituent is larger than hydrogen—as would be the case with bicyclic phosphate

*trans*-**2.10.7**, this unfavorable 1,5-interaction is large enough to prevent the reaction from proceeding.

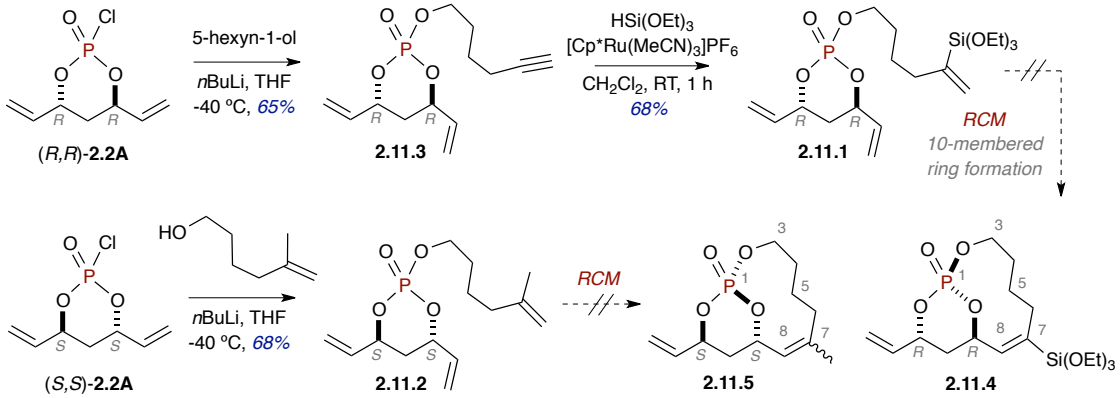
**Figure 2.4** *X-ray crystallographic analysis of cis-**2.10.6**.*




This *E*-selectivity of the P-tether mediated RCM to afford bicyclo[7.3.1]phosphates via the formation of a C7–C8 double bond within the bicyclic framework was somewhat surprising, as the RCM of analogous monocyclic Si-tethered systems proceeds with predominantly *Z*-configured olefin formation—even within larger rings (*vide supra*).[41] Therefore, in addition to providing a viable means for the generation of bicyclic phosphate **2.9.2** en route to dictyostatin (Scheme 2.9), there was some interest in attempting to perturb the stereoselectivity of the phosphate tether-mediated RCM to provide 10- and 11-membered rings to broaden the scope of the molecules accessible by this method. Thus, trienes **2.11.1** and **2.11.2** were chosen as model substrates to assess the effect of olefin substitution on the phosphate tether-mediated RCM to generate bicyclo[7.3.1]phosphates (Scheme 2.11). [17,42]

Enantiomeric monochlorophosphates (*R*,*R*)-**2.2A** and (*S*,*S*)-**2.2A**[3] were added to the lithium alkoxides of 5-hexyn-1-ol and 5-methyl-5-hexen-1-ol, respectively, to afford alkynyl diene **2.11.3** and triene **2.11.2** in 65% and 68% yield, respectively (Scheme 2.11). Subsequent hydrosilylation of **2.11.3**, using conditions developed by Trost and Ball,[43]

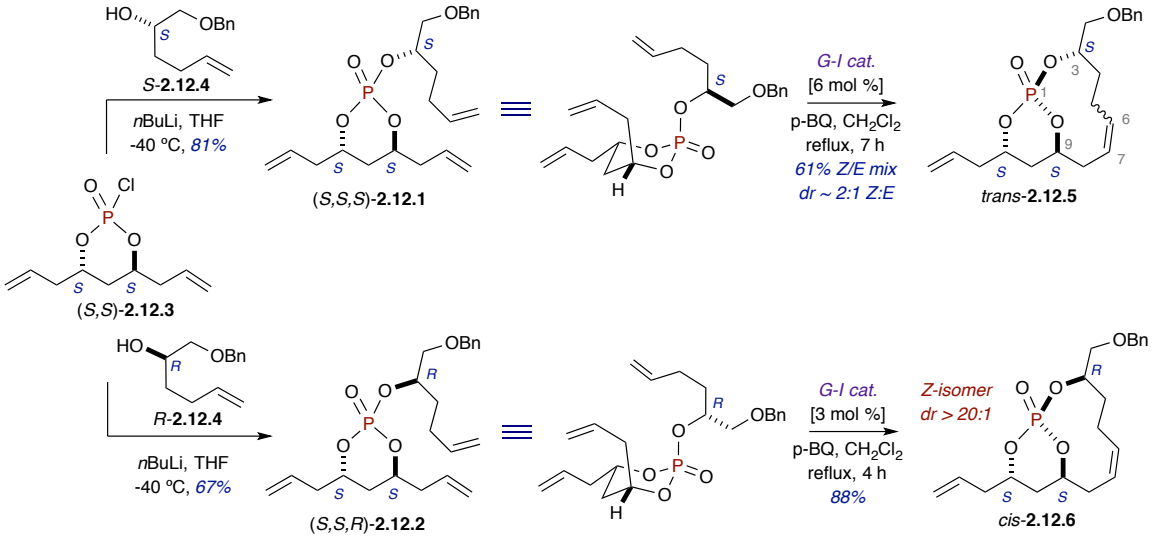
provided vinyl silyloxy-containing triene **2.11.1** in moderate yield. Unfortunately, though a variety of catalysts and reaction conditions were attempted, the formation of bicyclo[7.3.1]phosphates **2.11.4** and **2.11.5** could not be achieved by RCM. With these results in hand, combined with those obtained in previous studies,[12,16] we hypothesized that the proximity of the forming olefin (C7–C8) to the bridgehead carbon (C9) of the resultant bicyclo[7.3.1]phosphate, in combination with C3-substitution, was a significant contributor to the success and stereoselectivity of the phosphate tether-mediated RCM. Moreover, it was conjectured that homologation of the $C_2$-symmetric dienediol used to generate the corresponding phosphate trienes could have important stereochemical and conformational effects on the synthesis of bicyclo[7.3.1]phosphates by virtue of increasing the distance between the forming olefin (now, C6–C7) and the bridgehead carbon (C9).




**Scheme 2.11** *Ring-closing metathesis to bicyclo[7.3.1]phosphates via formation of C7–C8-trisubstituted olefins.*

To assess this hypothesis, diastereomeric phosphate trienes **2.12.1** and **2.12.2** were synthesized from the coupling of monochlorophosphate (*S*,*S*)-**2.12.3**[12,16] and the

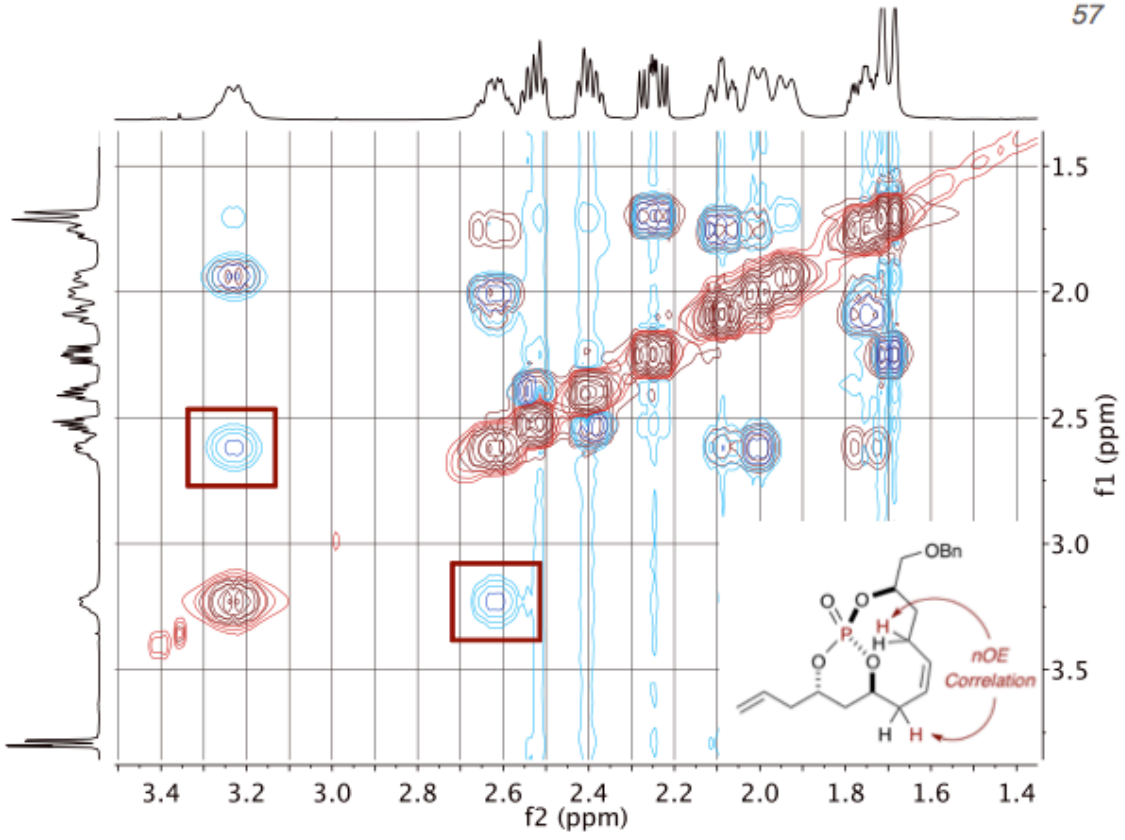
corresponding chiral, non-racemic olefinic alcohols (*S*)-**2.12.4**[44] and (*R*)-**2.12.4**,[45] respectively (Scheme 2.12). Treatment of triene **2.12.1** with Grubbs first generation catalyst (G-I), added in 1 mol % portions over 7 hours (6 mol %, total), provided the corresponding bicyclo[7.3.1]phosphates *trans*-**2.12.5**[46] in 61% combined yield of a separable 2:1 mixture of *Z*/*E*-stereoisomers (with *Z*-*trans*-**2.12.5** as the major stereoisomer).[47] Notably, the formation of the analogous equivalent of this *trans*-bicyclo[7.3.1]phosphate via C7–C8 olefin formation was unsuccessful under a variety of RCM conditions,[16] suggesting that the extension of the forming olefin from C7–C8 to C6–7 could provide for conformational flexibility that allows for the reaction of the latter to proceed (albeit with lower stereoselectivity). Conversely, RCM of triene **2.12.2** with G-I (3 mol %) provided *Z*-olefin-containing *cis*-**2.12.6** in 88% as a single stereoisomer (dr > 20:1).




**Scheme 2.12** *Synthesis of bicyclo[7.3.1]phosphates via formation of C6–C7-disubstituted olefins.*

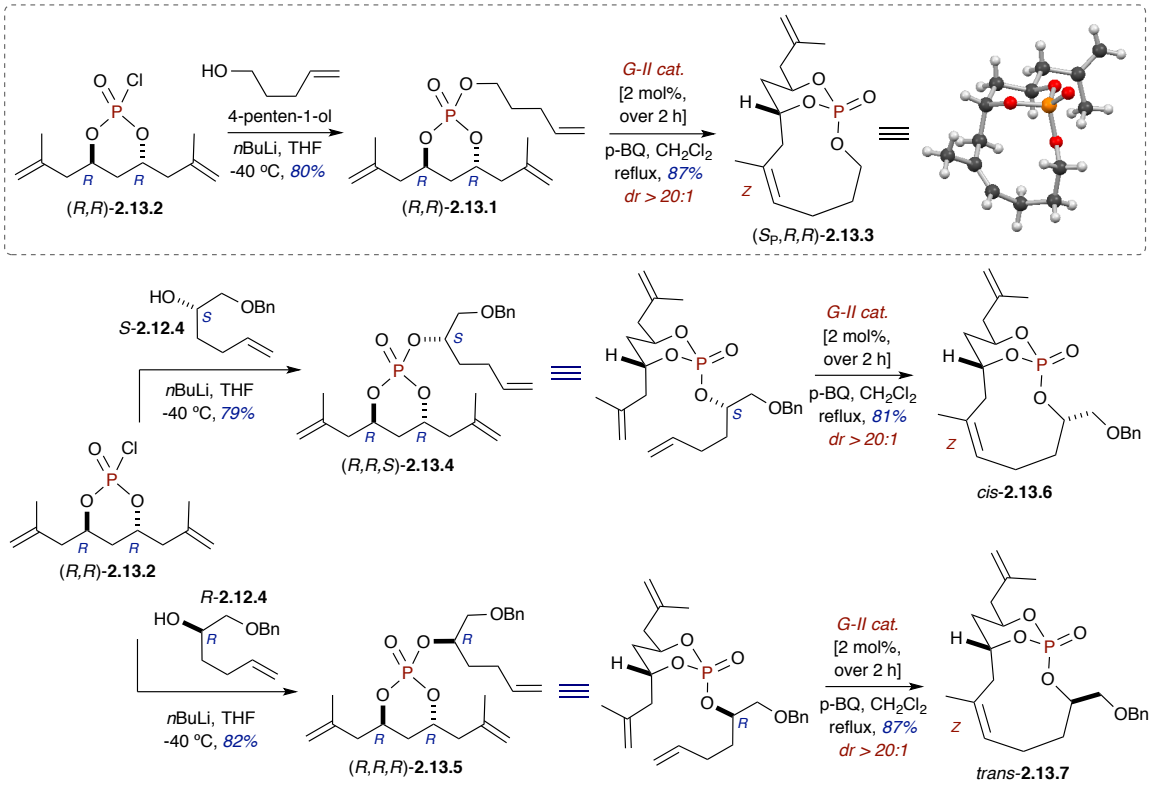
Olefin stereochemistry (*Z*- versus *E*-configuration) was determined by detailed NMR analysis of both coupling constants of olefinic protons (which often overlapped and complicated coupling constant assignment), proton shift, and NOESY correlation of olefinic protons and/or vinylic methylene ($CH_2$) signals. Unambiguous definition of each proton signal was necessary to arrive at meaningful conclusions, and as such, it is included in the experimental section corresponding to this chapter (see Chapter 5). The alkyl region of a sample spectra is shown in Figure 2.5 (for *cis*-**2.12.6**), where clear NOESY correlation (blue) between allylic C–H signals confirms *Z*-olefin configuration—

**Figure 2.X** *NMR analysis to identify the stereochemical outcome of RCM event – bicyclo[5.3.1]phosphates (cis-**2.12.6**).*



as only groups in *cis*-orientation will show through-space correlations. In addition, due to the complexity of the $^{1}$H NMR spectra for each of these large ring-containing bicyclic phosphates, it was often helpful to superimpose the 2-dimensional COSY spectra (shown in red in Figure 2.5) onto the NOESY spectra (shown in blue in Figure 2.5) of a single molecule, to quickly differentiate through-space correlation from vicinal/geminal correlation.

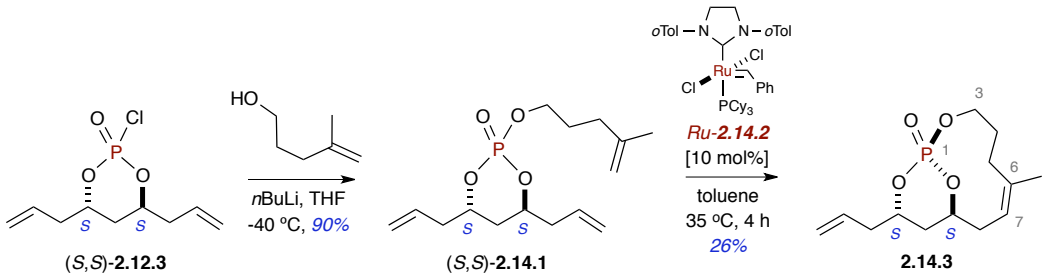
In addition to C3-substitution, olefin substitution was introduced to assess the effect—if any—on the success and stereochemical outcome of RCM to generate bicyclo[7.3.1]phosphates. To separate the effect of olefin substitution from C3-substitution, we first synthesized simple triene **2.13.1** via the coupling of monochlorophosphate (*R*,*R*)-**2.13.2**[12,16] with 4-penten-1-ol (Scheme 2.13). Exposure of **2.13.1** to Grubbs second-generation catalyst (G-II) provided the corresponding bicyclic phosphate **2.13.3** as the Z-isomer in 87% yield. Olefin configuration was confirmed by X-ray crystallographic analysis, as shown in Scheme 2.13.[48] Interestingly, C3-substitution had little effect on the outcome of RCM for this set of bicyclo[7.3.1]phosphates, as the treatment of diastereomeric trienes **2.13.4** and **2.13.5** with G-II catalyst provided the expected bicyclic phosphates *cis*-**2.13.6** and *trans*-**2.13.7** in 81% and 87% yields, respectively, with excellent *Z*:*E*-diastereomeric ratios in each case. However, this substitution had a significant effect on the $^{1}$H and $^{13}$C NMR of *trans*-**2.13.7**, as high temperatures (95°C, DMSO-$d_6$) and extended experiment times were required to partially resolve proton signals and properly identify short, broad carbon signals (See Experimental Data in Chapter 5 of this thesis).




**Scheme 2.13** *Synthesis of bicyclo[7.3.1]phosphates via formation of C6–C7-trisubstituted olefins.*

Finally, monochlorophosphate (*S,S*)-**2.12.3** was coupled with 4-methyl-4-penten-1-ol to provide triene **2.14.1**, armed with olefin substitution on the alcohol cross-partner, in 90% yield (Scheme 4). Triene **2.14.1** was treated with *o*-tolyl-Grubbs second-generation catalyst-variant Ru-**2.14.2**,[49] in toluene at 35°C, to generate bicyclic phosphate **2.14.3** in 26% yield as the *Z*-isomer—in addition with a significant amount of oligomerization by-product. It should be noted that a number of reaction conditions were attempted to decrease the amount of oligomerization of **2.14.1** that occurs upon treatment with metathesis catalyst. However, extended reaction times and portion-wise addition of catalyst only led to an increase in oligomerization and a decrease in yield, presumably

due to the Type I nature of the mono-substituted olefins in pseudo-$C_2$-symmetric triene **2.14.1** and the resultant exocyclic olefin in bicyclic phosphate **2.14.3**.[50]

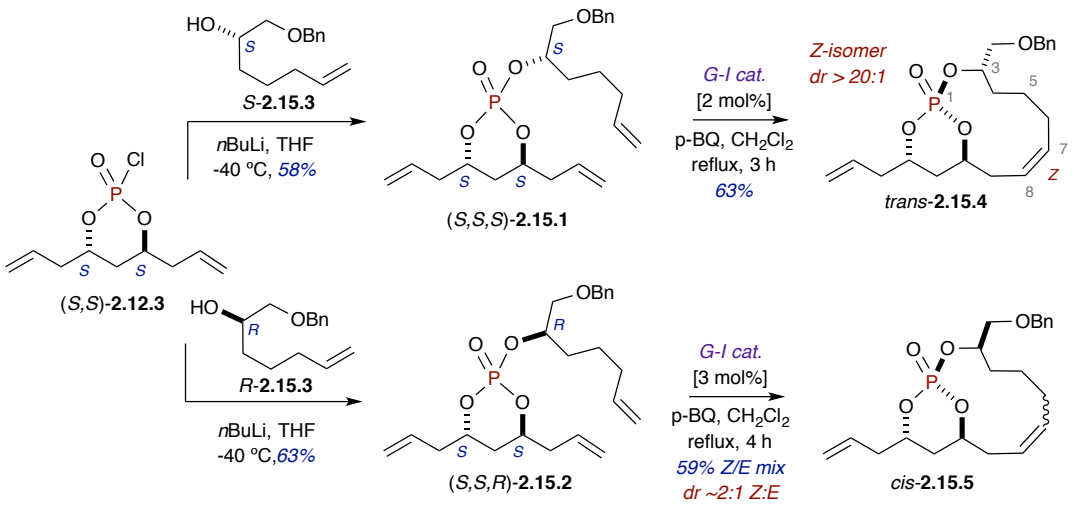



**Scheme 2.14** *Synthesis of bicyclo[7.3.1]phosphates via formation of C6–C7-trisubstituted olefins.*

*2.2.3 Synthesis of Bicyclo[8.3.1]phosphates*

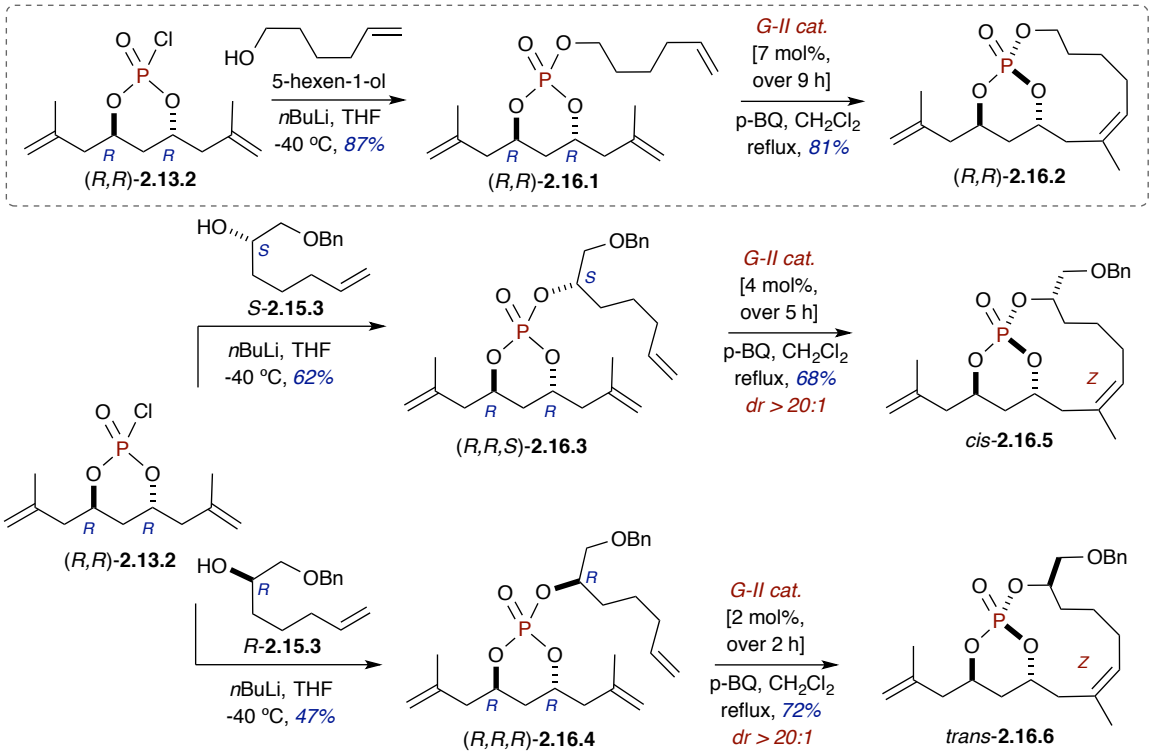
The method was extended to include the synthesis of bicyclo[8.3.1]phosphates via the formation of a C7–C8 olefin in order to determine the effects of C3-stereochemistry, olefin substitution, and proximity of the forming olefin to the bridgehead carbon (C10) on the success and stereochemical outcome of the RCM event. Studies commenced with the synthesis of diastereomeric trienes **2.15.1** and **2.15.2** from monochlorophosphate **2.12.3** and the corresponding chiral, non-racemic olefin-containing alcohols (*S*)-**2.15.3**[39] and (*R*)-**2.15.3**[51] (Scheme 2.15). Triene **2.15.1** was treated with G-I catalyst, in refluxing methylene chloride, to provide *trans*-**2.15.4** in 63% as the *Z*-isomer (dr > 20:1). Conversely, the exposure of triene **2.15.2** to RCM conditions afforded bicyclic phosphates *cis*-**2.15.5** as an inseparable mixture of *Z*/*E*-isomers (dr = 2:1 *Z*:*E*).[52] These results were somewhat surprising, as the stereoselectivity of RCM to afford these C3-substituted bicyclo[8.3.1]phosphates was opposite the selectivity observed for the

analogous bicyclo[7.3.1]phosphate systems (*trans*-**2.12.5** and *cis*-**2.12.6**, Scheme 2, *vide supra*).




**Scheme 2.15** *Synthesis of bicyclo[8.3.1]phosphates via formation of C7–C8-disubstituted olefins.*

The effect of olefin substitution on the success and stereochemical outcome of RCM to bicyclo[8.3.1]phosphates was next examined. In this regard, simple triene **2.16.1** was synthesized, in excellent yield, from the coupling of (*R,R*)-**2.13.2** and 5-hexen-1-ol (Scheme 2.16). Exposure of **2.16.1** to G-II catalyst (7 mol % over 9 hours) provided the corresponding bicyclo[7.3.1]phosphate **2.16.2** with exclusive *Z*-selectivity (dr > 20:1, as observed by NMR). To examine the effect of C3-substitution in these systems, we next synthesized diastereomeric phosphate trienes **2.16.3** and **2.16.4** from the coupling of monochlorophosphate **2.13.2** with chiral, non-racemic alcohols (*S*)-**2.15.3** and (*R*)-**2.15.3**, respectively. Treatment of phosphate trienes **2.16.3** and **2.16.4** with G-II catalyst provided the expected products (*cis*-**2.16.5** and *trans*-**2.16.6**) in good yield and selectivity.

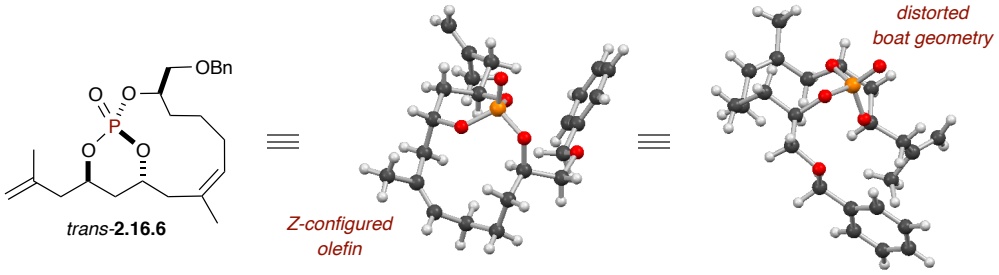



**Scheme 2.16** *Synthesis of bicyclo[8.3.1]phosphates via formation of C7–C8-disubstituted olefins*.

X-ray crystallographic analysis of *trans*-**2.16.6** confirmed the stereochemical result determined by NMR analysis (Figure 2.6). Interestingly, while the X-ray structures of every bicyclic phosphate obtained to date reveal an expected chair-conformation of the 6-membered ring of the bicyclic phosphate, the X-ray crystallographic analysis of *trans*-**2.16.6** show a distorted boat geometry of the 6-membered ring, compensated for by a distorted tetrahedral geometry of the phosphate itself. In addition, the C3-substituent is directed away from the concave interior of the bicyclic phosphate. Taken collectively, this X-ray, in combination with experimental observation (gathered for both 10- and 11-membered ring formation, *vide supra*), suggest that C3-substitution could have a

significant effect on large ring dynamics that influences the stereoselectivity of the RCM event.

**Figure 2.6** *X-ray confirmation of olefin stereochemistry and revelation of distorted boat geometry in trans-***2.16.6**.




## 2.3 Conclusion

In summary, phosphate tether-mediated RCM to provide a variety of *P*-stereogenic bicyclo[4.3.1]-, bicyclo[5.3.1]-, bicyclo[7.3.1]- and bicyclo[8.3.1]phosphates is reported. Taken collectively, these results suggest that C3-substitution, olefin substitution, the proximity of the forming olefin to the bridgehead carbon of resultant the bicyclic phosphate are all important factors in the success and stereochemical outcome of the RCM event. In addition, the bicyclic phosphates generated in this report represent an interesting class of macrocyclic phosphates with potential synthetic and biological utility as small molecule probes. Future efforts are aimed at understanding how ring-size and stereochemical complexity of bicyclo[n.3.1]phosphates affects the reactivity profile of each bicyclic phosphate, particularly as it relates to the addition of nitrogen-, oxygen-, and sulfur-based nucleophiles to phosphorus or phosphate-activated carbons.

## 2.4 Special Acknowledgment

The author acknowledges that portions of this chapter, including the preliminary Introduction and Results and Discussion sections, are reprinted, in part, or adapted from the following publications, with permission from the corresponding publishers:

1. Chegondi, R.; Maitra, S.; Markley, J. L.; Hanson, P. R. Phosphate-Tether-Mediated Ring-Closing Metathesis for the Preparation of Complex 1,3-anti-Diol-Containing Subunits. *Chem. Eur. J.* **2013**, *19*, 8088–8093, Copyright 2013, with permission from Wiley.

2. Maitra, S.; Markley, J. L.; Chegondi, R.; Hanson, P. R. Phosphate Tether-Mediated Ring-Closing Metathesis for the Generation of Medium to Large, P-Stereogenic Bicyclo[n.3.1]phosphates. *Tetrahedron* **2015**, *71*, 5734–5740, Copyright 2015, with permission from Elsevier.

3. Markley, J. L.; Maitra, S.; Hanson, P. R. Phosphate Tether-Mediated Ring-Closing Metathesis for the Generation of P-Stereogenic, Z-Configured Bicyclo[7.3.1]- and Bicyclo[8.3.1]phosphates. *J. Org. Chem.* **2016**, *81*, 899–911, Copyright 2016, with permission from American Chemical Society publications.

## 2.5 References Cited


[1] For an excellent review on reversible, covalent bonding and induced intramolecularity as it relates to catalysis, see: Tan, K. L. Induced Intramolecularity: An Effective Strategy in Catalysis. *ACS Catal.* **2011**, *1*, 877–886.

[2] (a) Evans, P. A. Temporary Silicon-Tethered Ring-Closing Metathesis Reactions in Natural Product Synthesis. In *Metathesis in Natural Product Synthesis*. Cossy, J.; Areniyadis, S.; Meyer, C., Eds.; Wiley-VCH,Weinheim, Germany, **2010**, p. 225–259; (b) Cusak, A. Temporary Silicon-Tethered Ring-Closing Metathesis: Recent Advances in Methodology Development and Natural Product Synthesis. *Chem. Eur. J.* **2012**, *18*, 5800–5824. (c) Evans, P. A.; Cui, J.; Buffone, G. P. Enantioselective Total Synthesis of the Potent Antitumor Agent (—)-Mucocin Using a Temporary Silicon-Tethered Ring-Closing Metathesis Cross-Coupling Reaction. *Angew. Chem. Int. Ed.* **2003**, *42*, 1734-1737. (d) Matsui, R.; Seto, K.; Fujita, K.; Suzuki, T.; Nakazaki, A.; Kobayashi, S. Unusual *E*-Selective Ring-Closing Metathesis To Form Eight-Membered Rings. *Angew. Chem. Int. Ed.* **2010**, *49*, 10068–10073.

[3] (a) Whitehead, A.; McReynolds, M. D.; Moore, J. D.; Hanson, P. R. Multivalent Activation in Temporary Phosphate Tethers: A New Tether for Small Molecule Synthesis. *Org. Lett.* **2005**, *7*, 3375–3378; (b) Whitehead, A.; McParland, J. P.; Hanson, P. R. Divalent Activation in Temporary Phosphate Tethers: Highly Selective Cuprate Displacement Reactions. *Org. Lett.* **2006**, *8*, 5025-5028; (c) Thomas, C. D.; McParland, J. P.; Hanson, P. R. Divalent and Multivalent Activation in Phosphate Triesters: A Versatile Method for the Synthesis of Advanced Polyol Synthons. *Eur. J. Org. Chem.* **2009**, 5487–5500. For a recent review on general RCM that contains a section on RCM to *P*-heterocycles, see: Maitra, S.; Chegondi, R.; Markley, J. L.; Hanson, P. R. General Ring Closing Metathesis. In *Handbook of metathesis: Application in Organic Synthesis,* 2nd ed.,

Vol. 2; Grubbs, R. H., O'Leary, D. J., Ed.; Wiley-VCH: Weinheim, Germany, **2015**; pp 1–170.

[4] Hanson, P. R.; Chegondi, R.; Nguyen, J.; Thomas, C. D.; Waetzig, J.; Whitehead, A. Total Synthesis of Dolabelide C: A Phosphate-Mediated Approach. *J. Org. Chem.* **2011**, *76*, 4358–4370.

[5] Chegondi, R.; Tan, M. M. L.; Hanson, P. R. Phosphate Tether-Mediated Approach to the Formal Synthesis of (–)-Salicylihalamides A and B. *J. Org. Chem.* **2011**, *76*, 3909–3916.

[6] Venukadasula, P. K. M.; Chegondi, R.; Maitra, S.; Hanson, P. R. A Concise, Phosphate-Mediated Approach to the Total Synthesis of (–)-Tetrahydrolipstatin. *Org. Lett.* **2010**, *12*, 1556–1559.

[7] Jayasinghe, S.; Venukadasula, P. K. M.; Hanson, P. R. An Efficient, Modular Approach for the Synthesis of (+)-Strictifolione and a Related Natural Product. *Org. Lett.* **2014**, *16*, 122–125.

[8] Chegondi, R.; Hanson, P. R. Synthetic Studies To Lyngbouilloside: A Phosphate Tether-mediated Synthesis of the Macrolactone Core. *Tetrahedron Lett.* **2015**, *56*, 3330–3333.

[9] In a manner similar to the naming system used in previous reports, we have generated a simplified set of identifiers that is a short-hand description of the IUPAC-designated names for each class of synthesized phosphate in order to emphasize the type of bicyclic structure formed after successful RCM. The proper names of each bicyclic phosphate are reported in the experimental section and corresponding supporting information. In addition, each proper name will be denoted as references throughout the manuscript. In this case, bicyclo[4.3.1]phosphates refers to "2,9,10-trioxa-1-phosphabicyclo(4.3.1)dec-4-ene 1-oxides."

[10] "Bicyclo[5.3.1]phosphates" refers to "2,10,11-trioxa-1-phosphabicyclo(5.3.1) undec-5-ene 1-oxides" and "2,10,11-trioxa-1-phosphabicyclo(5.3.1)undec-4-ene 1-oxides."

[11] "Bicyclo[7.3.1]phosphates" refers to "2,12,13-trioxa-1-phosphabicyclo(7.3.1)tridec-7-ene 1-oxides" and "2,12,13-trioxa-1-phosphabicyclo(7.3.1)tridec-6-ene 1-oxides."

[12] Chegondi, R.; Maitra, S.; Markley, J. L.; Hanson, P. R. Phosphate-Tether-Mediated Ring-Closing Metathesis for the Preparation of Complex 1,3-*anti*-Diol-Containing Subunits. *Chem. Eur. J.* **2013**, *19*, 8088–8093.

[13] The term "diastereoselective," while seemingly unintuitive, refers to the newly formed stereogenic center at phosphorus, which forms stereoselectively based upon the inherent stereochemistry of chiral, non-racemic, $C_2$-symmetric, 1,3-*anti*-diene diol utilized in the reaction; for a detailed discussion on this selectivity, see references 3a–c. Essentially, this term describes the diastereoselective RCM that results in the formation of a stereogenic phosphorus atom from RCM precursor trienes that are pseudo-$C_2$-symmetric.

[14] "Bicyclo[6.3.1]phosphates" refers to "2,11,12-trioxa-1-phosphabicyclo(6.3.1)dodec-5-ene 1 oxides" and "2,11,12-trioxa-1-phosphabicyclo(6.3.1)dodec-6-ene 1-oxides."

[15] "Bicyclo[8.3.1]phosphates" refers to "2,13,14-trioxa-1-phosphabicyclo(8.3.1)tetra-dec-8-ene 1 oxides" and "2,13,14-trioxa-1-phosphabicyclo(8.3.1)tetra-dec-7-ene 1 oxides."

[16] Maitra, S.; Markley, J. L.; Chegondi, R.; Hanson, P. R. Phosphate Tether-Mediated Ring-Closing Metathesis for the Generation of Medium to Large, *P*-Stereogenic Bicyclo[n.3.1]phosphates. *Tetrahedron* **2015**, *71*, 5734–5740.

[17] Markley, J. L.; Maitra, S.; Hanson, P. R. Phosphate Tether-Mediated Ring-Closing Metathesis for the Generation of *P*-Stereogenic, *Z*-Configured Bicyclo[7.3.1]- and Bicyclo[8.3.1]phosphates. *J. Org. Chem.* **2016**, *81*, 899–911.

[18] Hoye, T. R.; Promo, M. A. Silicon Tethered Ring-Closing Metathesis Reactions for Self- and Cross-Coupling of Alkenols. *Tetrahedron Lett.* **1999**, *40*, 1429–1432.

[19] Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. A Series of Well-Defined Metathesis Catalysts – Synthesis of $[RuCl_2(=CHR')(PR_3)_2]$ and Its Reactions. *Angew. Chem. Int. Ed.* **1995**, *34*, 2039–2041.

[20] Hoye, T. R.; Eklov, B. M.; Jeon, J.; Khoroosi, M. Sequencing of Three-Component Olefin Metatheses: Total Synthesis of Either (+)-Gigantecin or (+)-14-Deoxy-9-oxygigantecin. *Org. Lett*. **2006**, *8*, 3383–3386.

[21] (a) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J., Jr.; Hoveyda, A. H. A Recyclable Ru-Based Metathesis Catalyst. *J. Am. Chem. Soc*. **1999**, *121*, 791−799; (b) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. Efficient and Recyclable Monomeric and Dendritic Ru-Based Metathesis Catalysts. *J. Am. Chem. Soc*. **2000**, *122*, 8168−8179.

[22] Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. Synthesis and Activity of a New Generation of Ruthenium-Based Olefin Metathesis Catalysts Coordinated with 1,3-Dimesityl-4,5-dihydroimidazol-2-ylidene Ligands. *Org. Lett.* **1999**, *1*, 953–956.

[23] Kozmin, S. A.; Marjanovic, J. Spirofungin A: Stereoselective Synthesis and Inhibition of Isoleucyl-tRNA Synthetase. *Angew. Chem. Int. Ed.* **2007**, *46*, 8854–8857.

[24] Hooper, A. M.; Dufour, S.; Willaert, S.; Pouvreau, S.; Pickett, J. A. Synthesis of (2*S*,7*S*)-Dibutyroxynonane, the Sex Pheromone of the Orange Wheat Blossom Midge, *Sitodiplosis mosellana* (Gehin) (Diptera: Cecidomyiidae), by Diastereoselective Silicon-Tethered Ring-Closing Metathesis. *Tetrahedron Lett.* **2007**, *48*, 5991–5994.

[25] Scalzullo, S. M.; Islam, R. U.; Morgans, G. L.; Michael, J. P.; van Otterlo, W. A. L. Ring-Closing Metathesis for the Synthesis of Novel 9- and 10-Membered Silicon-Containing Benzo-Fused Heterocycles. *Tetrahedron Lett.* **2008**, *49*, 7403–7405.

[26] (a) Tullis, J. S.; Vares, L.; Kann, N.; Norrby, P.-O.; Rein, T. Reagent Control of Geometric Selectivity and Enantiotopic Group Preference in Asymmetric Horner-

Wadsworth-Emmons Reactions with meso-Dialdehydes. *J. Org. Chem.* **1998**, *63*, 8284–8294; b) Rychnovsky, S. D.; Yang, G.; Hu, Y.; Khire, U. R. Prins Desymmetrization of a $C_2$-Symmetric Diol: Application to the Synthesis of 17-Deoxyroflamycoin. *J. Org. Chem.* **1997**, *62*, 3022–3023; c) Rychnovsky, S. D.; Griesgraber, G.; Zeller, S.; Skalitzky, D. J. Optically pure 1,3-diols from (2*R*,4*R*)- and (2*S*,4*S*)-1,2:4,5-diepoxypentane. *J. Org. Chem.* **1991**, *56*, 5161–5169.

[27] Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. Synthesis and Activity of a New Generation of Ruthenium-Based Olefin Metathesis Catalysts Coordinated with 1,3-Dimesityl-4,5-dihydroimidazol-2-ylidene Ligands. *Org. Lett.* **1999**, *1*, 953–956.

[28] (a) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J., Jr.; Hoveyda, A. H. A Recyclable Ru-Based Metathesis Catalyst. *J. Am. Chem. Soc*. **1999**, *121*, 791−799; (b) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. Efficient and Recyclable Monomeric and Dendritic Ru-Based Metathesis Catalysts. *J. Am. Chem. Soc*. **2000**, *122*, 8168−8179.

[29] Venukadasula, P. K. M.; Chegondi, R.; Maitra, S.; Hanson, P. R. A Concise, Phosphate-Mediated Approach to the Total Synthesis of (–)-Tetrahydrolipstatin. *Org. Lett.* **2010**, *12*, 1556–1559.

[30] Davoille, R. J.; Rutherford, D. T.; Christie, S. D. R. Homologation of Allylic Alcohols. An Approach to Cyclic and Acyclic Polyoxygenated Compounds. *Tetrahedron Lett.* **2000**, *41*, 1255–1259.

[31] It was found that the use of very dry THF and freshly titrated n-BuLi significantly affects the yields of these couplings. As such, the moderate yields reported in references 12 and 16 for several of these transformations were likely due to solvent impurities (water content) and not inherent difficulty with the phosphorylations reactions themselves (as evident by the much higher yields of coupling reported in reference 17).

[32] The *cis*/*trans*-descriptors in *cis*-**2.7.5** and *trans*-**2.7.4** refer to the relative stereochemistry between the substituents at C3 and C6 in the bicyclo[4.3.1]phosphates.

[33] All X-ray crystallographic data has been submitted to the Cambridge Crystallographic Data Centre, and the structure for *trans*-**2.7.4** was assigned the following deposition number: 905668.

[34] Hashimura, K. Tomita, S.; Hiroya, K.; Ogasawara, K. A Stereocontrolled Route to Both Enantiomers of the Necine Base Dihydroxyheliotridane via Intramolecular 1,3-Dipolar Addition Using the Same Chiral Precursor. *J. Chem. Soc., Chem. Commun.* **1995**, 2291–2292.

[35] Maitra, S. Phosphate Tether-Mediated Metathesis Studies and Application Towards Natural Product Synthesis. Ph.D. Thesis, University of Kansas, Lawrence, KS, June 2016.

[36] (a) Pettit, G. R.; Chicacz, Z. A.; Gao, F.; Boyd, M. R.; Schmidt, J. M. *J. Chem. Soc. Chem. Commun.* **1994**, 1111–1112; (b) Paterson, I.; Britton, R.; Delgado, O.; Gardner, N. M.; Meyer, A.; Naylor, G. J.; Poullennec, K. G. *Tetrahedron* **2010**, *66*, 6534–6545; (c) Shin, Y.; Fournier, J. H.; Fukui, Y.; Brückner, A. M.; Curran, D. P. *Angew. Chem.* **2004**, *116*, 4734–4737; *Angew. Chem. Int. Ed.* **2004**, *43*, 4634–4637; (d) Zhu, W.; Jiménez, M.; Jung, W. H.; Camarco, D. P.; Balachandran, R.; Vogt, A.; Day, B. W.; Curran, D. P. *J. Am. Chem. Soc.* **2010**, *132*, 9175–9187; e) O'Neil, G. W.; Phillips, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 5340–5341; (f) Ramachandran, P. V.; Srivastava, A.; Hazra, D. *Org. Lett.* **2007**, *9*, 157–160; (g) Jogalekar, A. S.; Damodaran, K.; Kriel, F. H.; Jung, W.-H.; Alcaraz, A. A.; Zhong, S.; Curran, D. P.; Snyder, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 2427–2436; (h) Gallon, J.; Esteban, J.; Bouzbouz, S.; Campbell, M.; Reymond, S.; Cossy, J. *Chem. Eur. J.* **2012**, *18*, 11788–11797 and references cited therein.

[37] Ying, M.; Roush, W. R. Studies on the synthesis of reidispongiolide A: stereoselective synthesis of the C(22)-C(36) fragment. *Tetrahedron* **2011**, *67*,

10274–10280.

[38] Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. A Series of Well-Defined Metathesis Catalysts – Synthesis of $[RuCl_2(=CHR')(PR_3)_2]$ and Its Reactions. *Angew. Chem. Int. Ed.* **1995**, *34*, 2039–2041.

[39] Ida, A.; Hoshiya, N.; Uenishi, J. Investigation of Pd(II)-Catalyzed Cyclization of Chiral θ-Hydroxy-α,β,γ,δ-unsaturated Dienol. *Heterocycles* **2015**, *90*, 1082–1093.

[40] All X-ray crystallographic data has been submitted to the Cambridge Crystallographic Data Centre, and the structure for *cis*-**2.10.6** was assigned the following deposition number: 1058400.

[41] (a) Hoye, T. R.; Promo, M. A. *Tetrahedron Lett.* **1999**, *40*, 1429–1432; (b) Scalzullo, S. M.; Islam, R. U.; Morgans, G. L.; Michael, J. P.; van Otterlo, W. A. L. *Tetrahedron Lett*. **2008**, *49*, 7403 –7405. (c) Urosa, A.; Marcos, I. S.; Díez, D.; Padrón, J. M.; Basabe, P. *J. Org. Chem.* **2015**, *80*, 6447–6455. (d) En route to the total synthesis of (+)-gigantecin, Hoye and coworkers observed an unexpected 11-membered RCM of a silicon-tethered intermediate to provide the corresponding monocycle with predominantly *Z*-olefin selectivity, see: Hoye, T. R.; Eklov, B. M.; Jeon, J.; Khoroosi, M. *Org. Lett.* **2006**, *8*, 3383–3386.

[42] The use of a removable silyl group to control the stereoselectivity of macrocyclic RCM was first published by Schreiber and Young in the following report: Wang, Y.; Jimenez, M.; Hansen, A. S.; Raiber, E.-A. Schreiber, S.; Young, D. W. Control of Olefin Geometry in Macrocyclic Ring-Closing Metathesis Using a Removable Silyl Group. *J. Am. Chem. Soc.* **2011**, *133*, 9196–9199.

[43] Trost, B. M.; Ball, Z. T. Alkyne Hydrosilylation Catalyzed by a Cationic Ruthenium Complex: Efficient and General *Trans* Addition. *J. Am. Chem. Soc.* **2005**, *127*, 17644–17655.

[44] Alam, M; Wise, C.; Baxter, C. A.; Cleator, E.; Walkinshaw, A. Development of a Robust Procedure for the Copper-Catalyzed Ring-Opening of Epoxides with Grignard Reagents. *Org. Proc. Res. Dev.* **2012**, *16*, 435–441.

[45] Takano, S.; Moriya, M.; Iwabuchi, Y. Ogasawara, K. Concise Synthesis of $C_2$-Symmetric *Trans*-2,5-Dioxymethylpyrrolidine Derivatives by Novel Cyclization. *Tetrahedron Lett.* **1989**, *30*, 3805–3806.

[46] The *cis*-/*trans*- descriptors in *cis*-**2.12.6** and *trans*-**2.12.5** refer to the relative stereochemistry between the substituents at C3 and C9 in the bicyclo[7.3.1]phosphates.

[47] Olefin stereochemistry (*Z*- versus *E*-configuration) was determined by detailed NMR analysis of both coupling constants of olefinic protons, proton shift, and NOESY correlation of olefinic protons and/or vinylic methylene ($CH_2$) signals. Unambiguous definition of each proton signal was necessary to arrive at meaningful conclusions, and as such, it is included in the Experimental Section corresponding to this chapter (See Chapter 5 of this thesis).

[48] All X-ray crystallographic data has been submitted to the Cambridge Crystallographic Data Centre, and the structures were assigned the following deposition numbers: **2.13.3** (1431827) and *trans*-**2.16.6** (1431826).

[49] Stewart, I. C.; Ung, T.; Pletnev, A. A.; Berlin, J. M.; Grubbs, R. H.; Schrodi, Y. Highly Efficient Ruthenium Catalysts for the Formation of Tetrasubstituted Olefins via Ring-Closing Metathesis. *Org. Lett*. **2007**, *9*, 1589–1592.

[50] Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. A General Model for Selectivity in Olefin Cross Metathesis. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.

[51] Ichimoto, I.; Ohotomo, Y.; Kirihata, M.; Tsuji, H.; Ueda, H. Stereoselective Synthesis of (–)-Patulolide B, a New Macrolide from a Strain of *Penicillium urticae*. *Chemistry Express* **1989**, *4*, 625–628.

[52] Diastereoselectivity was determined by NMR analysis (1H and proton-decoupled 13P NMR). The 2:1 mixture of *Z*- and *E*-isomers of ***cis*-2.15.5** was purified to a 10:1 mixture of the major stereoisomer (*Z*-configured) to the minor stereoisomer (*E*-configured, confirmed by LC-MS) for full characterization and confirmation of the olefin configuration.

# Chapter 3

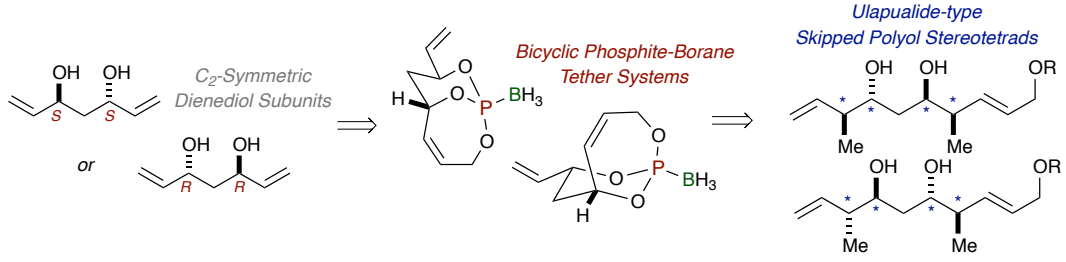
*P-Stereogenic Bicyclo[4.3.1]Phosphite Boranes: Tunable P-Tether Systems for the Synthesis of 1,3-Skipped Polyol Stereotetrads*

## 3.1 Introduction

The facile formation of complex intermediates from simple core fragments common to a variety of natural products is central to the development of effective strategies for the synthesis of biologically active small molecules. In particular, those methods which couple a variety of simple and complex chemical fragments in a mild, manipulatable fashion and allow for the facile generation of molecular complexity represent some of the most efficient strategies to accomplish this goal. Over the past decade, our group has focused on the development of phosphate triester tether-mediated methods for the two-directional synthesis of complex polyols from $C_2$-symmetric dienediol substrates.[1] These methods have served as key transformations in a number of total and formal syntheses [see Chapter 1 of this thesis],[2] and on-going efforts continue to exploit the inherent chemistry of bicyclic phosphate triesters—particulary their ability to mediate multiple transformations in one-pot sequential processes—in the two-directional synthesis of complex polyols.[3] Additionally, current efforts in our group have aimed at exploring alternative tripodal tether systems in order to identify unique reactivity profiles which may be utilized in the synthesis of chemical scaffolds that would be difficult, expensive, or laborious to access via previously reported methods. In this regard, this chapter presents the use of bicyclic P(III)-phosphite borane tethers for the desymmetrization of $C_2$-symmetric, 1,3-*anti*-diols to provide 1,3-skipped polyol stereotetrads. These studies highlight the *P*-tether systems' ability to facilitate chemoselective cross-metathesis reactions with Type I and Type II olefins,[4] divergent oxidation strategies that allow for the transformation of the P–B bond to P=O or P=S

bonds, and a stereocontrolled iterative $S_N2'$-cuprate displacement protocol that marries the chemistry of phosphite borane tethers with that of their all oxygen-containing counterparts to generate stereotetrads that were previously inaccessible via phosphate tether strategies alone (Figure 3.1). In addition to providing unique *P*-containing scaffolds with interesting potential as biological probes, this method may serve as a useful alternative to aldol-like coupling strategies[5] or other asymmetric crotylation[6] protocols to provide functionalized 1,3-skipped polyol intermediates for the synthesis of complex natural products.

**Figure 3.1** *Bicyclic phosphite borane triesters as temporary tethers for the synthesis of complex polyols.*

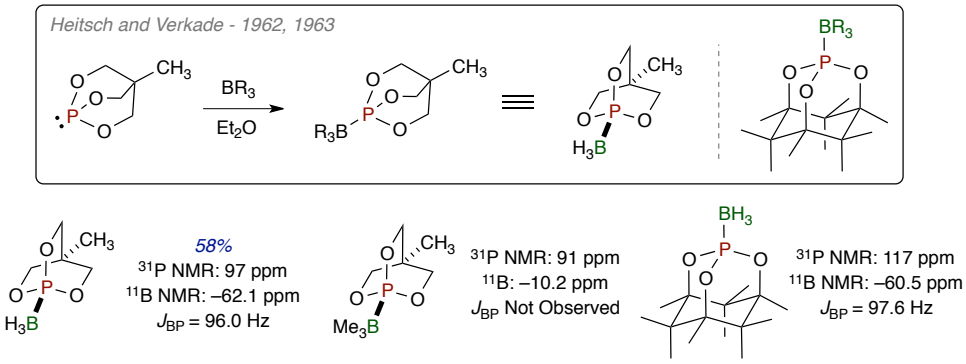



3.1.1 *Introduction to Borane-Complexed Phosphite Triesters*

Historically, the complexation of P(III)-compounds (phosphines, phosphites, phosphinites, phosponites, etc.) with boranes to generate oxidatively stable intermediates has been used as a means to generate and store large numbers of phosphite ligands for eventual application in transition-metal catalysis.[7] The first bicyclic, phosphite borane triesters were reported by Heitsche and Verkade in 1962,[8] where caged bicyclic phosphites were prepared and complexed with a variety of Lewis acidic boranes—including $BH_3$, $B_3H_7$, $B(CH_3)_3$, and $BF_3$—though only the $BH_3$ complex was stable

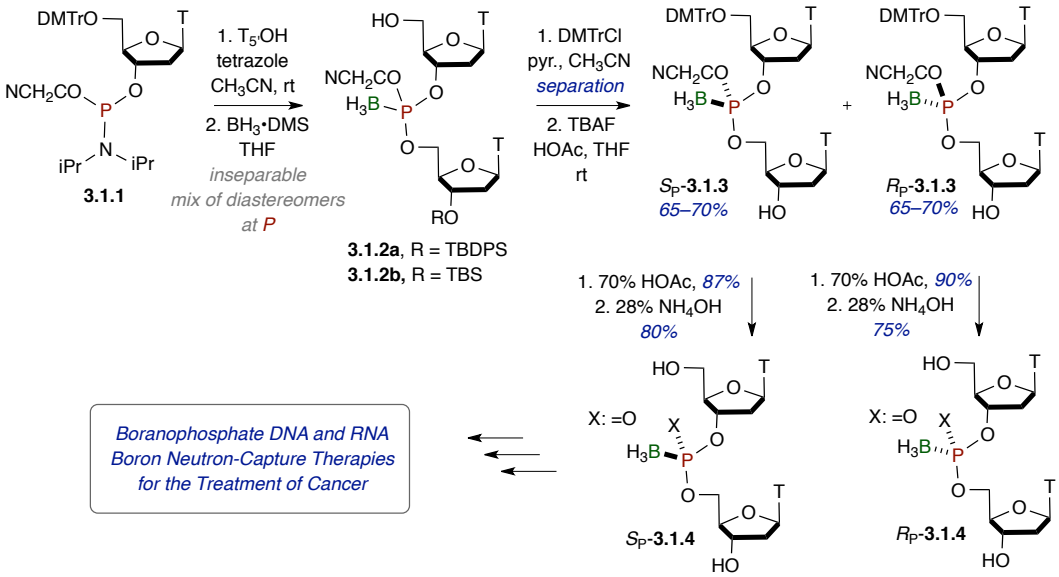
enough to be isolated from the reaction mixture (Figure 3.2). The authors later published a detailed study of the $^{1}H$, $^{31}P$, and $^{11}B$ NMR characteristics of several of these compounds in 1964,[9] noting that no P–B coupling was observed for the weaker Lewis acid-Lewis base complexes (phosphites with $BMe_3$ or $BF_3$) due to proposed rapid ligand exchange.

**Figure 3.2** *Borane complexes of polycyclic phosphites and corresponding NMR properties.*




In addition to protection strategies for the synthesis of phosphite ligands, borane complexes with phosphites or phosphonites have been used as intermediates en route to synthetically useful *H*-phosphonates [$(RO)_2PHO$], *H*-phosphinates [(RO)RPHO], and biologically relevant boranophosphates [$(RO)_2(BH_3)P{=}O$]. In 1998, Jin and Just reported the use of phosphite borane adducts en route to the synthesis of *P*-diastereomeric mixtures of dithymidine boranophosphates—valuable intermediates for the formation of boranophosphate DNA or RNA with promising applications in the treatment of cancer.[10,11] Tetrazole-facilitated coupling of commercially available 5'-(4,4'-dimethoxytrityl)-thymidine phosphoroamidite **3.1.1** with 3'-protected thymidine (R = TBDPS or TBS), followed by boronation with $BH_3$•DMS and concomitant DMTr-

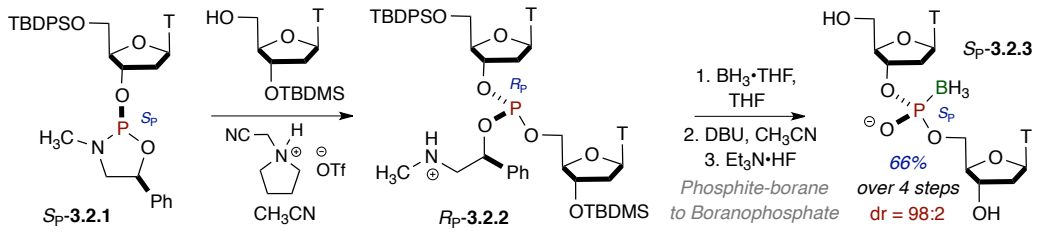
deprotection, afforded the corresponding phosphite boranes **3.1.2a** (R = TBDPS) and **3.1.2b** (R = TBS) as inseparable mixtures of diastereomers at phosphorus (Scheme 3.1). DMTr-protection of the primary alcohol allowed for chromatographic separation of *P*-diastereomers, and subsequent silyl-deprotection with TBAF provided $S_P$-**3.1.3** and $R_P$-**3.1.3** in 65–70% yield. Finally, high yielding DMTr-deprotection with acetic acid and exposure of the resultant phosphite borane triesters to concentrated ammonium hydroxide generated the corresponding boranophosphates $S_P$-**3.1.4** and $R_P$-**3.1.4** in excellent overall yield.




**Scheme 3.1** *Phosphite borane complexes as intermediates en route to boranophosphate dithymidines.*

Similarly, in 2006, Wada and coworkers published the use of phosphite borane triesters as intermediates en route to diastereopure $R_P$- and $S_P$-dithymidine boranophosphates via a method more amenable to solid phase synthesis than stereoselective syntheses previously described.[12] Diastereomerically pure 5'-*O*-(*tert*-

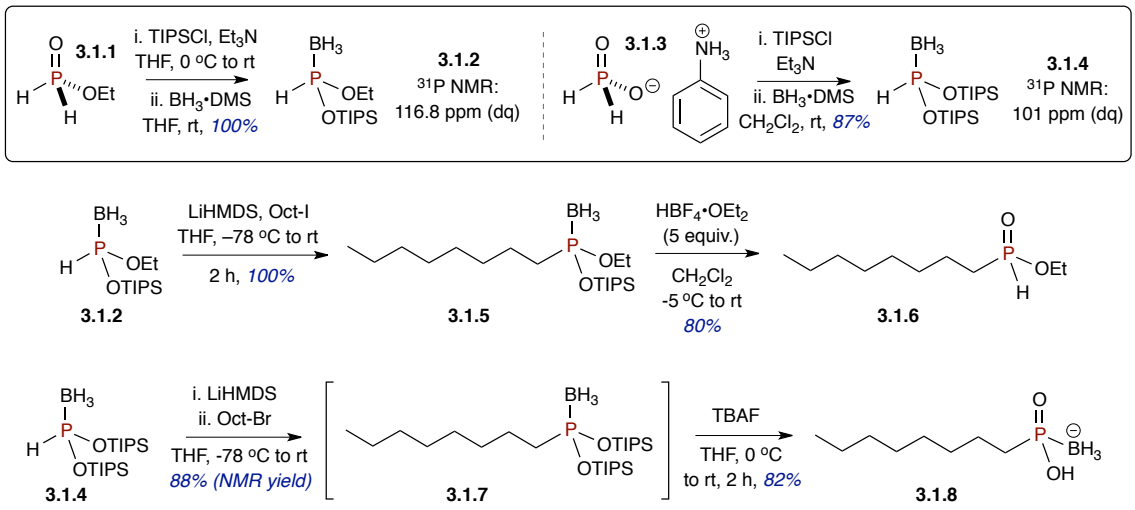
butyldiphenylsilyl)thymidine 3'-*O*-oxazaphospholidine $S_P$-**3.2.1**[13] was coupled with 3'-*O*-TBDPS-thymidine, in the presence of an ammonium triflate activator, to provide $R_P$-**3.2.2**, resulting in inversion of stereochemistry at phosphorus (Scheme 3.2). Treatment of phosphite **3.2.2** with $BH_3$•THF afforded the intermediate phosphite borane triester that was smoothly converted to boranophosphate $S_P$-**3.2.3** (DBU, then $Et_3N$•HF) in 66% yield over 4 steps (dr = 98:2). This in-solution protocol was successfully adapted to solid-phase synthesis of $S_P$-**3.2.3** in the same publication.




**Scheme 3.2** *Stereoselective synthesis of phosphite borane complexes as intermediates en route to diastereopure boranophosphate oligonucleosides.*

In 2008, Montchamp and coworkers reported the synthesis of *O*-silyl-*H*-phosphite borane complexes [$(R^1O)(R^2O)P(BH_3)H$] and their use as synthetic intermediates to generate alkylated phosphinite-boranes, *H*-phosphonates, and boranophosphates (Scheme 3.3).[14] *O*-Silyl-*H*-phosphite borane complexes were prepared in one step from the corresponding *H*-phosphonates. In this manner, *in situ*-generated ethyl phosphinate[15] (**3.3.1**) was exposed to TIPSCl, in the presence of triethylamine, followed by borane protection with $BH_3$•DMS, to provide **3.3.2** in quantitative isolated yield. Correspondingly, commercially available anilinium hypophosphite (AHP, **3.3.3**) was exposed to similar conditions to afford *O,O'*-disilyl-*H*-phosphite borane **3.3.4** in 87% isolated yield. Base-promoted alkylation of these *H*-phosphite boranes allowed for the

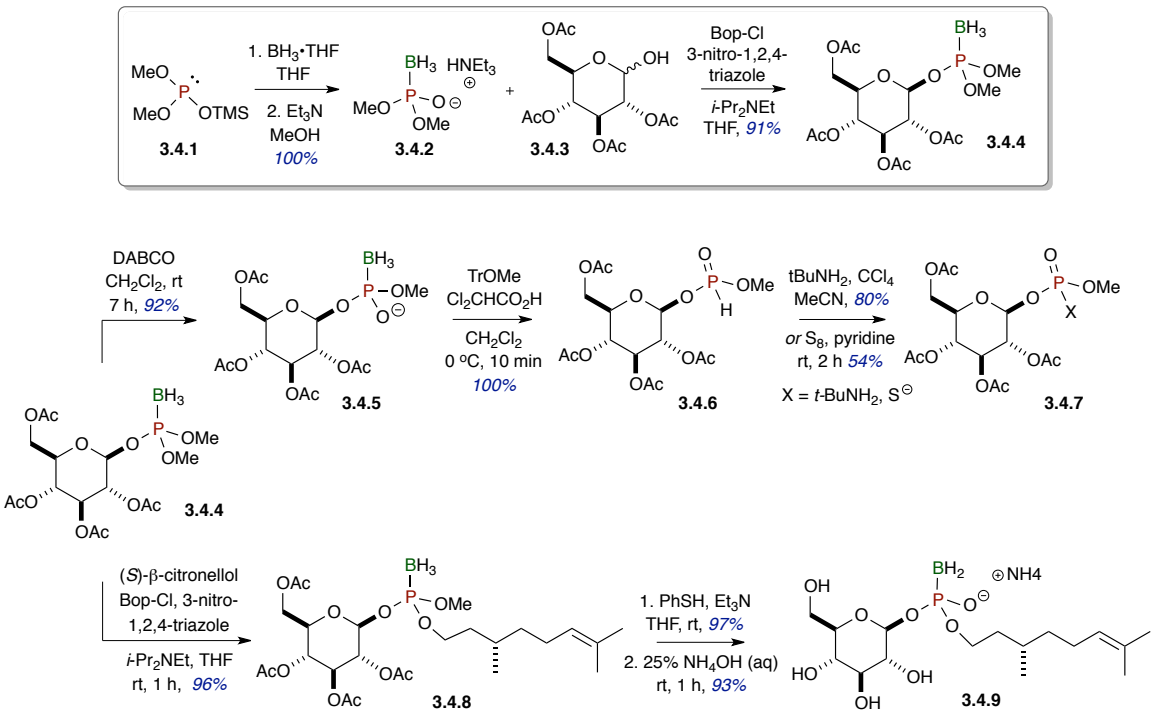
generation of a number of phosphinite-borane intermediates, which can be further transformed into either *H*-phosphinates or boranophosphates. In this regard, **3.3.2** was treated with LiHMDS, followed by addition of octyliodide, to provide phosphinite-borane **3.3.5** in quantitative yield. Subsequent oxidation of **3.3.5** with tetrafluoroboric acid etherate then afforded the corresponding *H*-phosphinate in 80% isolated yield. Similarly, treatment of **3.3.4** with LiHMDS, followed by octyl-bromide, provided phosphinite-borane **3.3.7**—which, when exposed to TBAF, generated the free boranophosphate in good overall yield.




**Scheme 3.3** *H-Phosphinite-borane complexes as synthetically useful H-phosphinate equivalents.*

In 2008, Wada and coworkers reported the use of glycosyl-dimethyl-phosphite borane triesters as intermediates for the synthesis of glycosyl boranophosphates, chemically stable *H*-phosphonate precursors for the formation of glycosyl phosphate analogues.[16] Boronation-desilylation of dimethyl trimethylsilyl phosphite **3.4.1,**[17] using $BH_3$•THF in THF followed by $Et_3N$ in methanol, provided salt **3.4.2** in quantitative yield

(Scheme 3.4).[18] Bop-Cl-mediated coupling of reducing sugar **3.4.3** with **3.4.2**, in the presence of catalytic 3-nitro-1,2,4-triazole (NT) and diisopropyl(ethyl)amine, afforded glycosyl phosphite borane **3.4.4** for further functionalization. Dimethyl phosphite borane **3.4.4** was demethylated with DABCO, and subsequent treatment with *in-situ*-generated trityl cation provided *H*-phosphonate **3.4.6** in excellent overall yield. The *H*-phosphonate intermediate (**3.4.6**) could be further elaborated to the phosphoramidate or phosphorothioate in 80% and 54% yield, respectively, as shown in Scheme 3.4. In addition, condensation of *S*-β-citronellol with dimethyl phosphite borane **3.2.4**, in the presence of BOP-Cl and catalytic NT, generated phosphite borane triester **3.4.8** in 96 yield; then, acetyl-deprotection, followed by phosphite borane exposure to ammonium



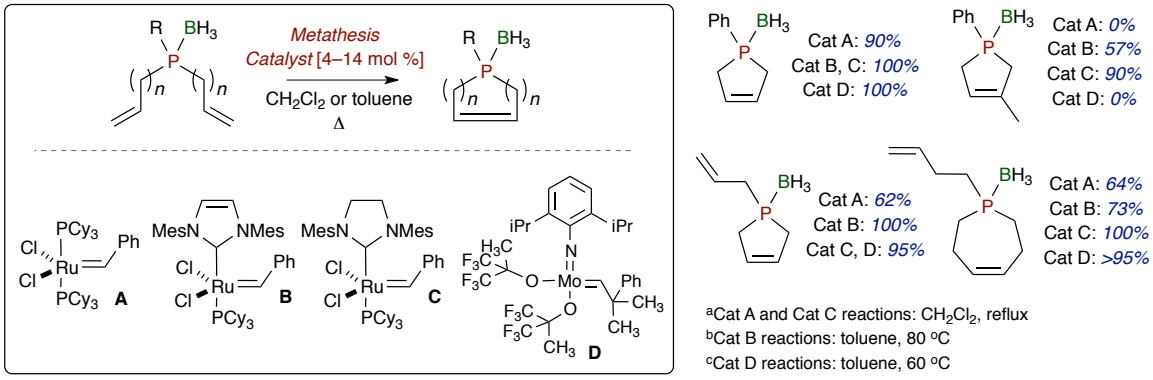

Scheme **3.4** *Glycosyl phosphite borane triesters to boranophosphate and H-phosphonate intermediates.*

hydroxide, yielded the corresponding boranophosphate **3.4.9** in 97% and 93% yields, respectively, highlighting the synthetic utility of both the intermediate phosphite borane triesters and their boranophosphate counterparts.

3.1.2 *Introduction to Metathesis Reactions with Borane-Complexed P(III)-Substrates*

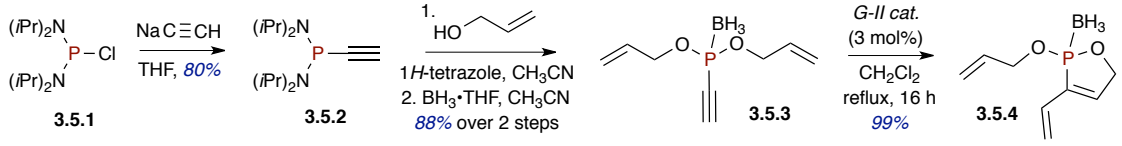
Though ring-closing metathesis of borane-complexed phosphite triesters is somewhat limited, RCM reactions of olefin-containing *P*(III)-borane complexes have garnered some attention over the past few decades. In 2000, Gouverneur and coworkers reported the first examples of ruthenium-catalyzed ring-closing metathesis on bis(alkenyl)phosphine-borane complexes.[19] Later, in 2003, the same group reported the use of both ruthenium- and molybdenum-based methathesis catalysts for similar substrates.[20] Results of these studies are summarized in Figure 3.3. Bis(alkenyl)phosphine-borane complexes were treated with four different metathesis catalysts (**A**–**D**), in refluxing $CH_2Cl_2$ or heated toluene for times ranging from 6–86 hours, to provide a variety of 5-, 6- (not shown), and 7-membered ring-containing, *P*-heterocyclic phosphine-borane compounds. Modification of ring size was fairly well-tolerated, particularly by catalysts **C** and **D**, though olefin functionalization led to marked

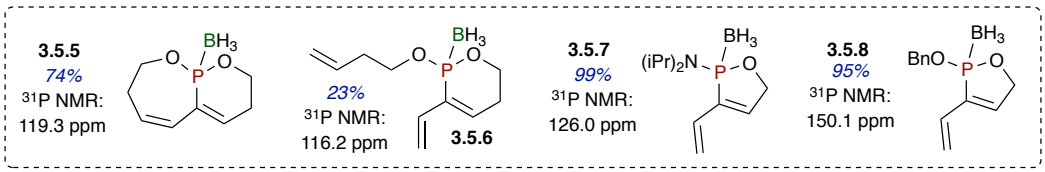
**Figure 3.3** *Ring-closing metathesis of phosphine-borane complexes.*



decrease in yields even under extended stir times with higher catalyst loadings.

In 2001, van Boom and coworkers reported the synthesis of mono- and bicyclic, borane-complexed P(III)-heterocycles via enyne-RCM and tandem enyne-RCM-RCM.[21] Nucleophilic addition of sodium acetylide to bis(diisopropylamino)chlorophosphine (**3.5.1**) generated (alkynyl)phosphine **3.5.2** in 80% yield (Scheme 3.5). Condensation of **3.5.2** with allyl alcohol (or an appropriate olefinic alcohol), in the presence of 1*H*-tetrazole, followed by boronation with $BH_3$•DMS, provided phosphonite-borane **3.5.3** in 88% yield. Subsequent ring-closing metathesis, catalyzed by Grubbs second-generation catalyst [G-II, $(ImesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$],[22] quantitatively transformed **3.5.3** into monocyclic phosphonite-borane **3.5.4**. Similarly, a number of mono- and bicyclic phosphonite-boranes were generated from the corresponding trienes in good yields.

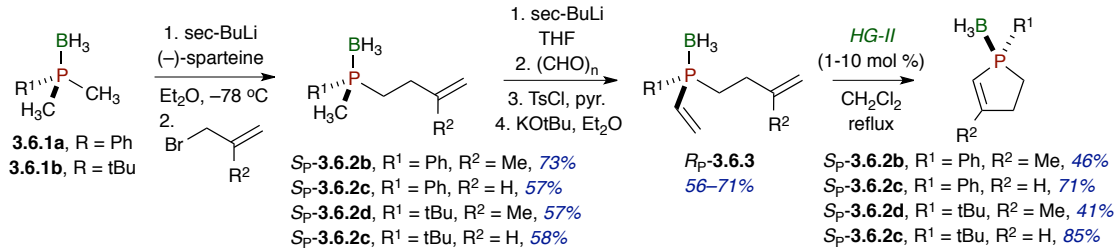



**Scheme 3.5** *Enyne-RCM of phosphinite-borane and phosphoroamidite-borane complexes.*

Recently, in 2013, O'Brien and coworkers published the first enantioselective synthesis of *P*-stereogenic vinylic phospholene boranes via a stereoselective deprotonation-alkylation-methenylation-RCM protocol.[23] Chiral, base-mediated deprotonation of phosphine boranes **3.6.1a** and **3.6.1b** with *sec*-butyllithium, in the

presence of (–)-sparteine (via a method developed by Evans and coworkers in 1995),[24] and subsequent allylation of the corresponding carbanion generated *P*-stereogenic phosphine-boranes **3.6.2** in moderate yield. A second deprotonation of the α-$CH_3$ with sec-BuLi, followed by trapping with paraformaldehyde, tosylation of the resultant alcohol, and elimination of the intermediate tosylate, then afforded dienes **3.6.3** in 56–73% yield. Finally, treatment of dienes **3.6.3** with catalytic Hoveyda-Grubbs second-generation catalyst (HG-II) in refluxing toluene provided monocyclic phospholene-boranes $S_P$-**3.6.2** in moderate to excellent yields (based on starting substrate).




**Scheme 3.6** *Asymmetric synthesis of P-stereogenic, monocyclic phospholene boranes via ring-closing metathesis.*

### 3.2 Results and Discussion

Over the past decade, our group has focused on the use of phosphate triester tether methods for the synthesis of 1,3-skipped polyol-containing natural products and natural product analogs,[2] and much like the synthetic community at large, we seek intriguing targets containing interesting chemical fragments to help catalyze method development and expansion. One such family of targets, the ulapualide polyketide natural products (Figure 3.4),[25] was found to contain a 1,3-skipped polyol stereotetrad comprised of a 1,3-*anti*-diol flanked by methyl-branched alkyl chains. We proposed that fragments of this

type could be synthesized utilizing a *P*-tether-mediated iterative alkylation strategy, similar to that outlined in Figure 3.5, where a regio- and diastereoselective $S_N2'$-cuprate displacement of an exocyclic leaving group, followed by a second regio- and diastereoselective $S_N2'$-cuprate displacement of the tether itself, would allow for the formation of functionalized versions of the desired intermediate.

**Figure 3.4** *Ulapualide family of natural products containing 1,3-skipped stereotetrads.*

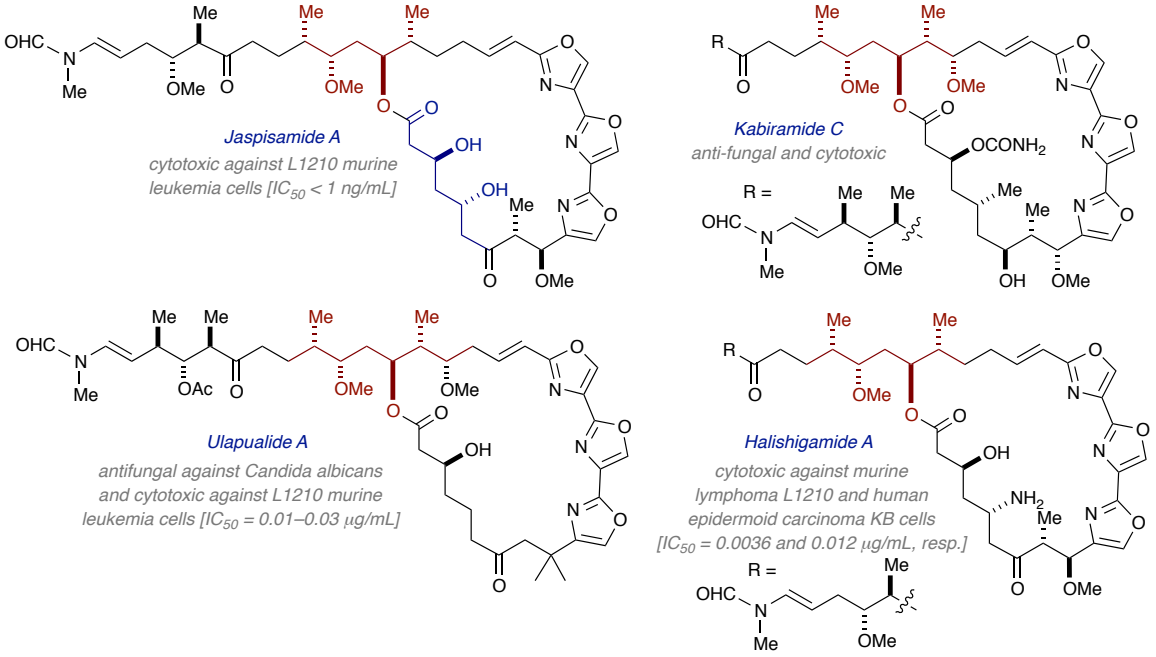
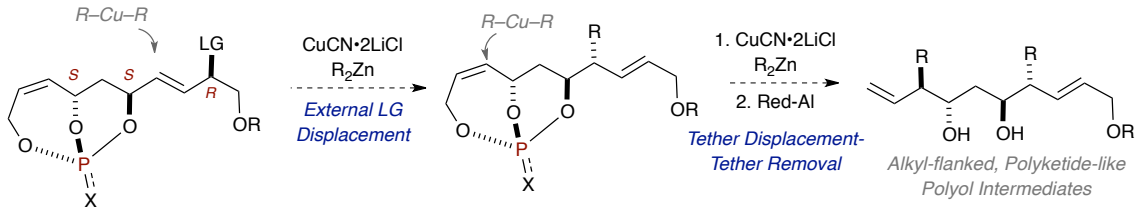
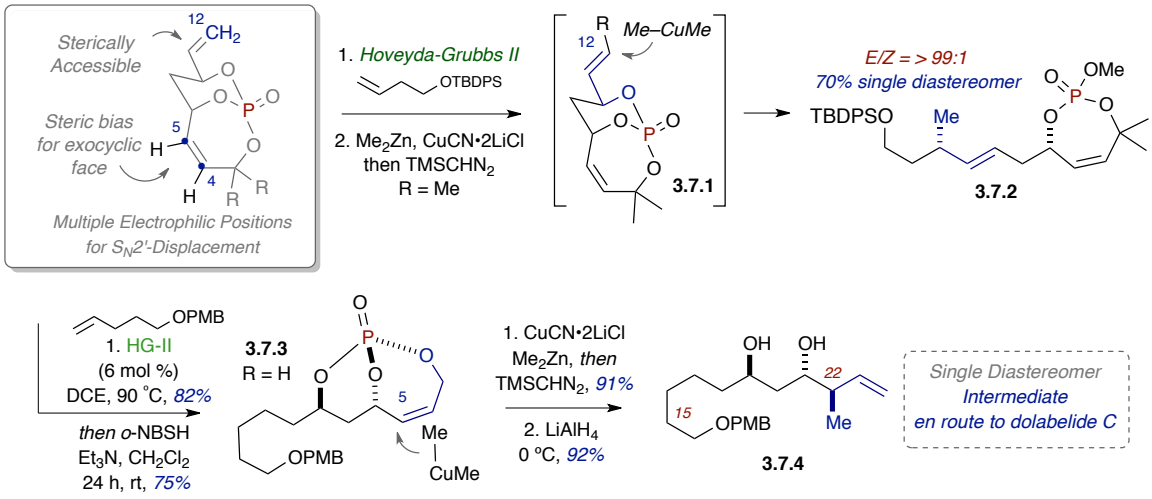



**Figure 3.5** *Proposed strategy to 1,3-skipped stereotetrads using P-tether mediated desymmetrization of $C_2$-symmetric, diene-containing diols*



Previous work in our laboratory examined the behavior of bicylic phosphate-containing molecules in the presence of *in-situ*-generated dialkyl cuprates. As shown in Scheme 3.7, the bicyclic phosphate activates multiple carbons for nucleophilic attack—highlighted are those carbons associated with allylic displacement of the phosphate. In 2007, Hanson and Whitehead reported that the $S_N2$'-cuprate addition of *in-situ*-generated dimethylcuprate to cross-metathesis product **3.7.1**, which contained both an endocyclic and exocyclic olefin, preferentially formed 7-membered, monocyclic phosphate **3.7.2**, in 70% yield and excellent selectivity via cuprate addition to C12 of the exocyclic olefin.[26] Correspondingly, when the exocyclic olefin is chemoselectively hydrogenated and the endocyclic olefin remains—as in bicyclic phosphate **3.7.3**, $S_N2$'-cuprate addition proceeds through addition to C5 of the olefin[27] to provide—after phosphoric acid methylation and tether removal—terminal olefin-containing diol **3.7.4**.

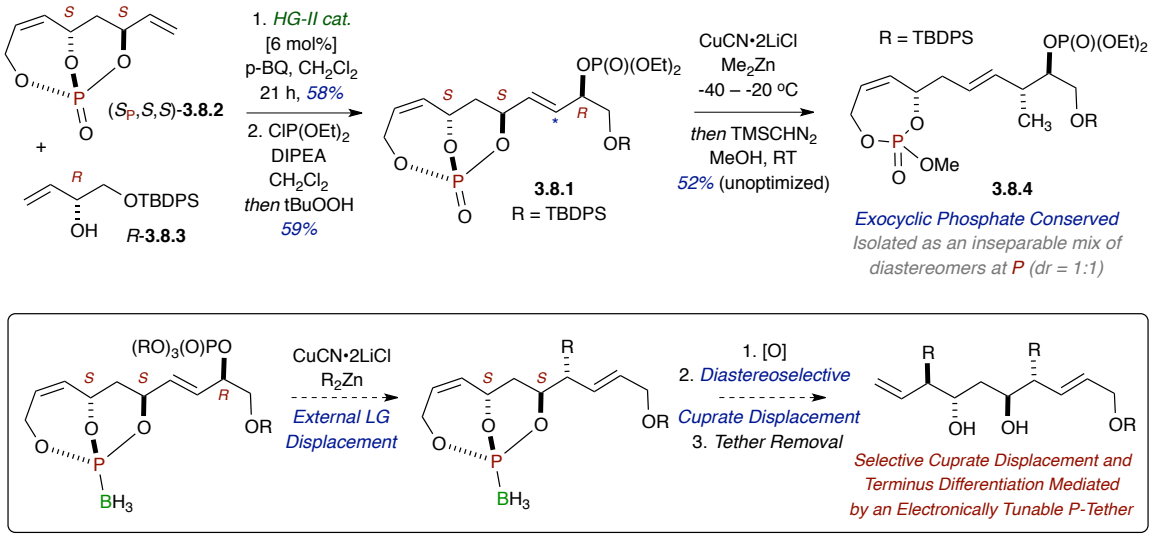



**Scheme 3.7** *Previous reports on stereoselective $S_N2$'-cuprate additions to biycyclic phosphates.*

Though these examples served as useful references for the general behavior of bicyclic phosphate in the presence of dialkyl cuprate, none of the previous reports examined substrates which contained an allylic, exocyclic leaving group in addition to the unsaturated bicyclic phosphate—and as such, would provide the necessary components to study a "competitive" cuprate addition similar to the one proposed in Figure 3.5. With this goal in mind, we synthesized di-phosphate **3.8.1** via cross metathesis of bicyclic phosphate ($S_P$,*S*,*S*)-**3.8.2**[1a] with chiral, non-racemic allylic alcohol *R*-**3.8.3**,[28] followed by phosphitylation-oxidation of the resultant alcohol, in moderate, unoptimized yield (Scheme 3.8). **3.8.1** was treated with *in-situ*-generated dimethyl cuprate (3 equiv) in THF at -40 $^{o}$C, followed by methylation of the resultant phosphoric acid, to provide the product corresponding to phosphate-tether displacement (**3.8.4**), in moderate yield as an inseparable mixture of diastereomers at the cyclic phosphorus.

With this result in hand, we proposed that the desired protocol presented in Figure 3.5 could be made viable by one of two possible scenarios: (i) a non-trivial optimization of conditions required to out-compete phosphate-tether displacement via judicious choice of generated cuprate, reaction conditions, and appropriate leaving group; or (ii) a modification of the tether, such that competitive $S_N2$'-cuprate addition favors the displacement of an external leaving group and subsequent modification of tether electronics could then favor a second selective cuprate displacement of the tether itself. We then proposed that a phosphite borane tether might provide the necessary electronic requirements for competitive cuprate displacement—since nucleophilic additions to carbinol carbons of other phosphite borane triesters are slow.[29] In addition, a phosphite

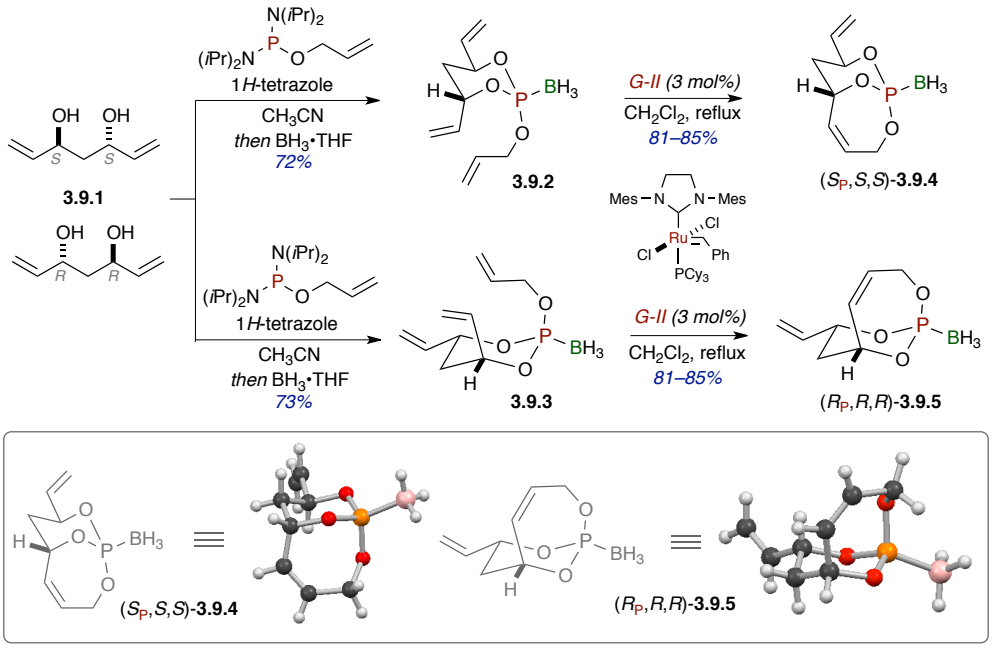
borane tether system would possess the appropriate electronic tunability that would allow for the formation of bicyclic phosphate from P-$BH_3$ precursors, since deprotection-oxidation strategies to provide P=O bonds from P–$BH_3$ bonds are known;[30] thus, a second diastereoselective cuprate displacement of the intermediate bicyclic phosphate obtained from the oxidation of the P-$BH_3$ precursor, followed by tether removal, would generate desired 1,3-skipped polyol-containing stereotetrads en route to the synthesis of more complex natural products.




**Scheme 3.8** *Competitive $S_N2'$-cuprate displacement of bicyclic phosphate in presence of exocyclic allylic phosphate leaving group and proposed strategy revisited.*

With this goal in mind, we first examined the ability of phosphite borane triesters to desymmetrize 1,3-*anti*-dienediols through a diastereoselective ring-closing metathesis analogous to that developed for the phosphate tether method.[1a] Enantiomeric dienediols (*R*,*R*)-**3.9.1** and (*S*,*S*)-**3.9.1** were coupled with commercially available allyl tetraisopropylphosphorodiamidite, in the presence of 1*H*-tetrazole, to provide the

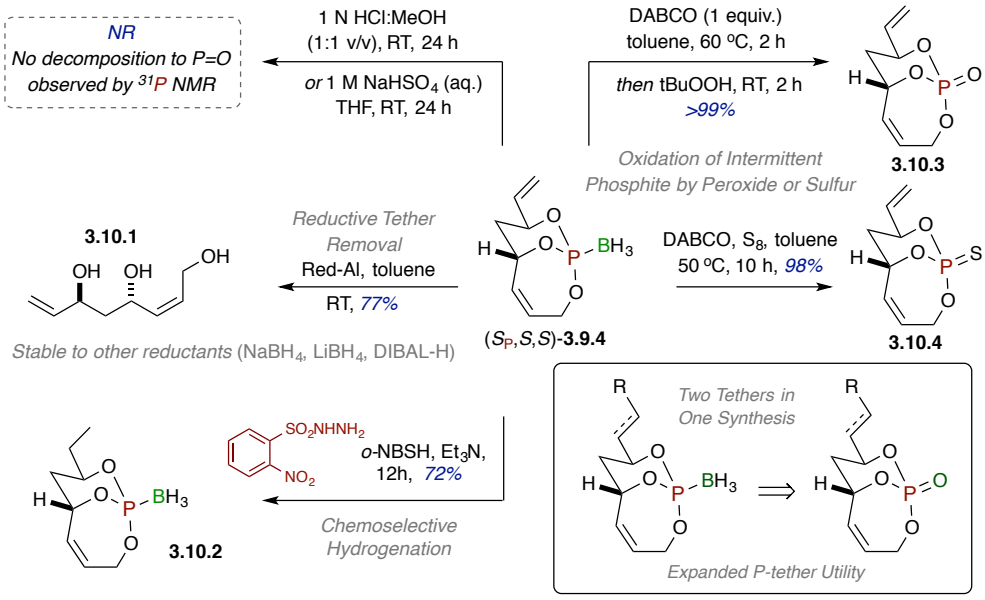
intermediate phosphite, which was subsequently protected by the addition of excess $BH_3$•THF to afford the corresponding trienes (*R*,*R*)-**3.9.1** and (*S*,*S*)-**3.9.1** in 73% and 72%, respectively (Scheme 3.9). It should be noted that these trienes were stable for storage under argon atmosphere at lower temperatures (<5 $^{o}$C) for greater than 1 year; however, extended times for chromatographic separation resulted in partial triene decomposition, even when eluent was doped with triethylamine (5–10%). Thus, purification of crude triene reaction mixture via filter column chromatography (silica, 15% EtOAc in hexanes) is required to separate triene from amine by-product that inhibits the following ring-closing metathesis reaction. RCM of trienes (*S*,*S*)-**3.9.2** and (*R*,*R*)-**3.9.3**, in the presence of G-II, afforded the corresponding bicyclic phosphite boranes ($S_P$,*S*,*S*)-**3.9.4** and ($R_P$,*R*,*R*)-**3.9.5** as off-white solids. These bicyclic phosphite boranes were stable when stored at low temperature for extended periods of time (>2 years) and were also stable to chromatographic separation without observable decomposition. X-ray crystallographic analysis[31] of ($R_P$,*R*,*R*)-**3.9.5** and ($S_P$,*S*,*S*)-**3.9.4** showed that each possess concave, caged structures similar to their all-*O*-containing phosphate counterparts, suggesting that the three-dimensional orientation of these substrates may allow for stereoselective additions to the internal olefin of the bicyclic phosphite borane systems.




**Scheme 3.9** *Synthesis of enantiomeric bicyclo[4.3.1]phosphite borane tether systems and corresponding X-ray crystal structures.*

In addition to column chromatography, the bicyclic phosphite borane ($S_P$,*S*,*S*)-**3.9.4** was found to be stable to acidic conditions common to a variety of work-up procedures (1 N HCl in MeOH, 1 M $NaHSO_4$ (aq) in THF, vigorous stirring with equal portions of EtOAc and saturated $NH_4Cl$ (aq)), though the complex readily decomposed upon treatment with hydroxide base (Scheme 3.10). Reductive tether removal using Red-Al provided the corresponding triol **3.10.1** in excellent yield, though bicyclic ($S_P$,*S*,*S*)-**3.9.4** was stable to a variety of other reductants/hydride sources (including $LiBH_4$, $NaBH_4$, and DIBAL-H). Chemoselective hydrogenation of the exocyclic olefin under diimide reaction conditions showed that, much like with the bicyclic phosphate, selective functionalization of the terminal, exocyclic olefin in the presence of the internal olefin is achievable (**3.10.2**). Most notably, a divergent oxidation strategy involving deprotection

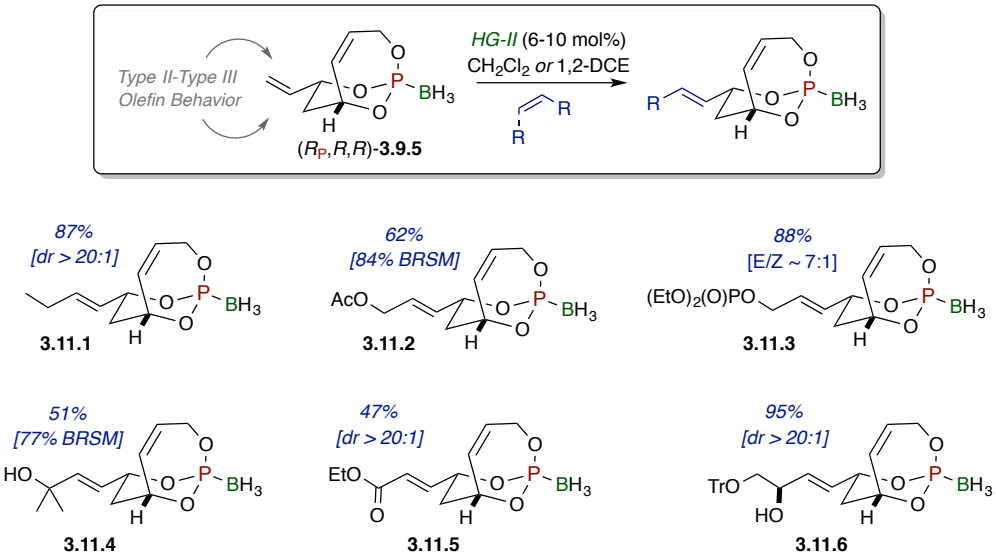
of the bicyclic phosphite with DABCO followed by oxidation with either tBuOOH or elemental sulfure ($S_8$) successfully generated both the bicyclic phosphate (P=O, **3.10.3**) and thiophosphate (P=S, **3.10.4**) from the phosphite borane precursor (**3.9.4**). This result was exciting, as a single synthetic strategy could first employ chemistry unique to the bicyclic phosphite borane and later, through oxidization of the P–$BH_3$ to the corresponding P=O, take advantage of chemistry unique to the bicyclic phosphate; thus, these two tether systems could be used separately or in tandem to rapidly build molecular complexity.




**Scheme 3.10** *Simple reactivity profile of bicyclo[4.3.1]phosphite borane complexes.*

In addition to chemoselective hydrogenation, the exocyclic olefin of the bicyclic phosphite borane (in this case, **3.9.5**) can be further functionalized via a selective cross-metathesis reaction, as shown in Scheme 3.11. Cross metathesis was successful with a variety of Type I and Type II olefin cross partners, and yields were found to range from moderate to excellent for the substrates screened. It should be noted that the *cis*-

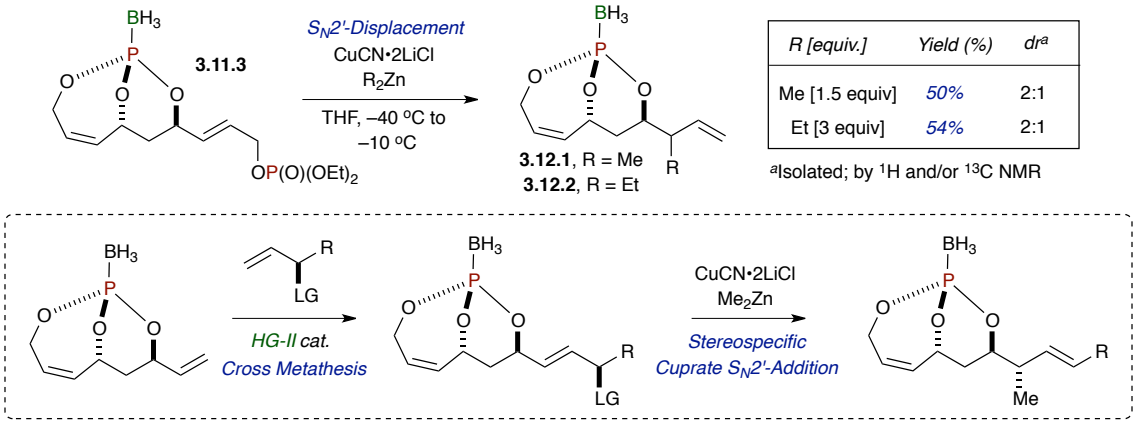
homodimers of Type I olefins allowed for higher conversions and yields than the mono-counterparts (for examples **3.11.1**, **3.11.2**, **3.11.3**), and lower yields were often the result of lower conversion, as evident by improved yields based on recovered starting material—which could be re-isolated and re-used in other reactions (examples **3.11.2** and **3.11.4**).




**Scheme 3.11** *Chemoselective cross-metathesis studies with Type I and Type II olefins.*

Cross-metathesis product **3.11.3** was chosen as a model substrate for competitive $S_N2'$-cuprate addition reactions and was treated with *in-situ*-generated dimethyl- and diethyl-cyanocuprates (1.5 equivalents and 3 equivalents, respectively) to generate bicyclic phosphite borane-containing alkylation products **3.12.1** and **3.12.2** in moderate yields (50% and 54%, respectively) and diastereomeric ratios of ~2:1 [major:minor] (Scheme 3.12). These results indicated that the bicyclic phosphite borane had only minor control over the stereoselectivity of the cuprate addition to the exocyclic olefin, and as such, implied that secondary substrate control via the stereospecific $S_N2'$-cuprate

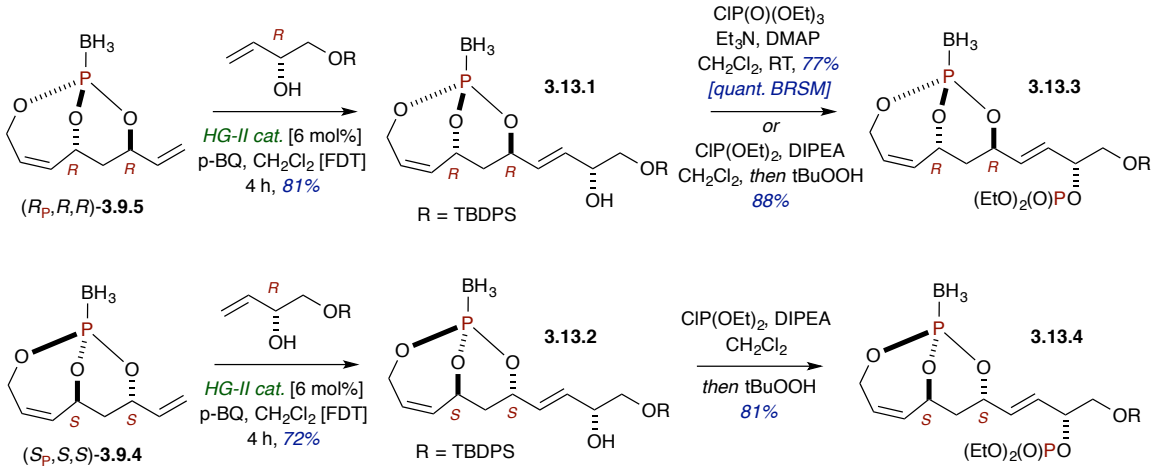
displacement of an exocyclic leaving group on a stereogenic carbon would allow for the generation of either the *syn*- or *anti*-alkylated products.




**Scheme 3.12** *Regioselective $S_N2'$-cuprate displacement of an exocyclic leaving group.*

With this goal in mind, we synthesized the bicyclic phosphite borane substrates bearing exocyclic allylic phosphates on stereogenic, secondary carbons as cuprate-addition precursors (Scheme 3.13). Direct metathesis with the pre-formed allylic phosphates proved to be ineffective at generating large amounts of product; however, sequential cross metathesis of either ($R_P$,*R*,*R*)-**3.9.5** or ($S_P$,*S*,*S*)-**3.9.4** with chiral, non-racemic *R*-**3.8.3**,[28] followed by phosphorylation or phosphitylation-oxidation, provided the desired precursors (**3.13.3** and **3.13.4**) in excellent yields over two steps. While this strategy was sufficient as a proof of concept, a second generation synthesis of these precursors using an RCM-CM-phosphorylation strategy would allow for the facile formation of diastereomeric **3.13.3** and **3.13.4** in two pots from simple dienediol precursors (4 total pots, overall), and future efforts in our group will involve the development of such one-pot sequential protocols mediated by the phosphite borane

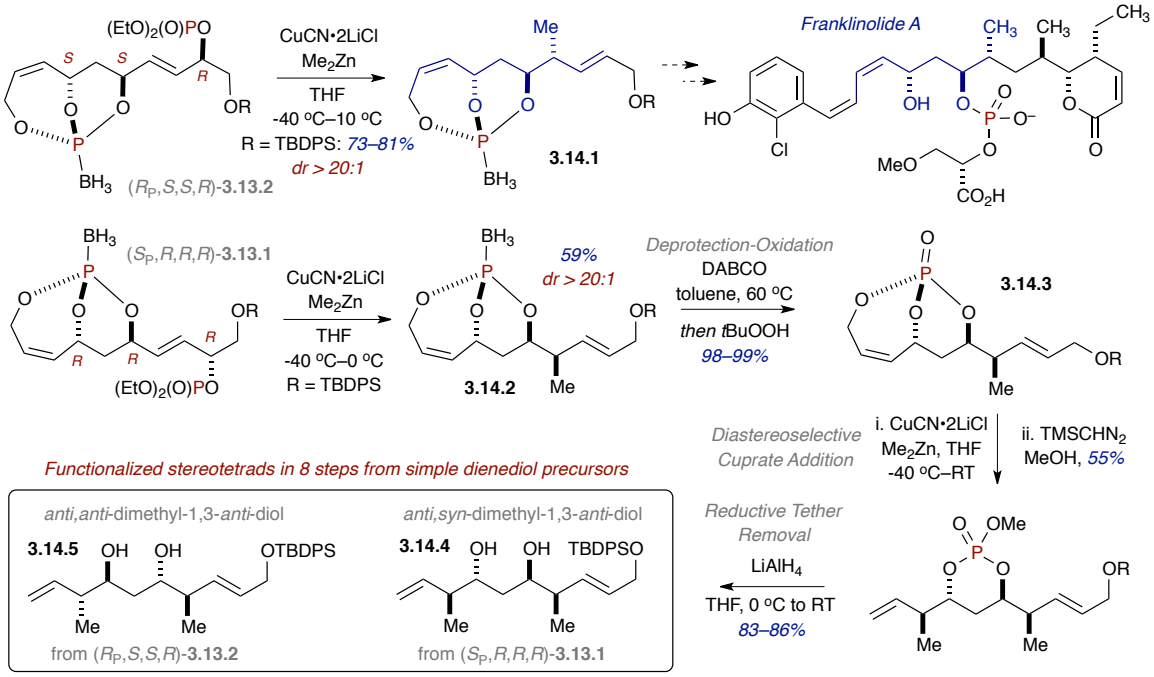
tether to streamline syntheses of these intermediates en route to the total synthesis of natural products.




**Scheme 3.13** *Synthesis of bicyclo[4.3.1]phosphite borane complexes bearing exocyclic allylic phosphates on stereogenic carbons.*

Phosphite borane phosphates **3.13.1** and **3.13.2** were next subjected to dimethylcuprate substitution conditions, and each generated the desired *anti*- or *syn*-alkylated bicyclic phosphite boranes **3.14.1** and **3.14.2** in moderate to excellent yields and excellent diastereoselectivities (dr > 20:1, Scheme 3.14). Though an iterative cuprate strategy resulting in the formation of 1,3-skipped polyol stereotetrads was the goal of this study, these mono-alkylated products are also useful intermediates in their own right, as **3.14.1** was initially designed to serve as an intermediate en route to the total synthesis of franklinolide A (the applicable backbone of which is highlighted in Scheme 3.14). Finally, oxidation of diastereomeric **3.14.1** and **3.14.2** to the corresponding bicyclic phosphates (only **3.14.3** shown below) in nearly quantitative yield, followed by a second stereospecific $S_N2'$-cuprate displacement of the bicyclic phosphate, methylation, and

subsequent reductive tether removal, afforded the desired 1,3-skipped polyol stereotetrads **3.14.4** and **3.14.5** in 8 pots from simple dienediol precursors. This strategy highlights the synthetic utility of this electronically tunable phosphorus tether by employing both bicyclic phosphite borane tether reactivity in tandem with bicyclic phosphate tether chemistry to generate substrates that were previously inaccessible via phosphate tether methods alone.



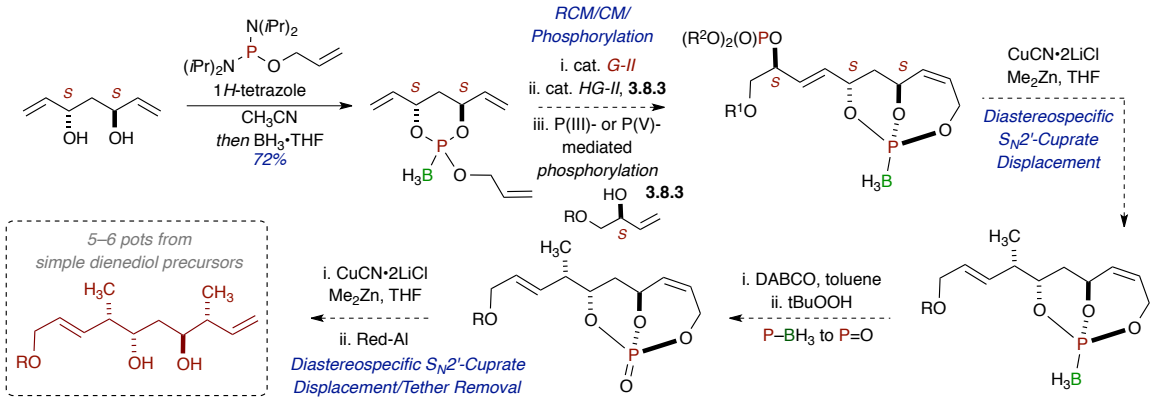

**Scheme 3.14** *Iterative $S_N2'$-cuprate addition protocol to provide functionalized 1,3-skipped polyol stereotetrads.*

### 3.3 Conclusions and Future Goals

In conclusion, this chapter presents the development of a new, electronically tunable *P*-tether system for the formation of 1,3-skipped polyol stereotetrads en route to the total synthesis of natural products. The bicyclic phosphite borane systems are stable

to chromatography, mild acid, and a number of hydride sources (and reductants other than Red-Al) and can be stored for extended periods of time at lower temperatures (>2 years at <5 °C). In an iterative cuprate strategy, this *P*-tether method allows for the initial desymmetrization of the 1,3-*anti*-dienediol, the regioselectivity of the first cuprate ($S_N2$'-displacement of an exocyclic leaving group), and the regio- and diastereoselectivity of the second cuprate displacement of the modified *P*-tether to generate stereotetrads that were previously inaccessible via other traditional phosphate tether strategies alone. Future work will include the incorporation of more complex tether pieces in triene formation (via the use of bis(diisopropylamino)chlorophosphine for tripodal coupling/phosphitylation) and the development of phosphite borane tether-mediated, one-pot sequential processes that will further streamline the facile formation of intermediates en route to the total synthesis of natural products.

**Figure 3.6** *Future plans for phosphite borane tether-mediated one-pot sequential protocols to 1,3-skipped polyol stereotetrads*



### 3.4 References Cited


[1] (a) Whitehead, A.; McReynolds, M. D.; Moore, J. D.; Hanson, P. R. Multivalent Activation in Temporary Phosphate Tethers: A New Tether for Small Molecule Synthesis. *Org. Lett.* **2005**, *7*, 3375–3378; (b) Waetzig, J. D.; Hanson, P. R. Temporary Phosphate Tethers: A Metathesis Strategy to Differentiated Polyol Subunits. *Org. Lett.* **2006**, *8*, 1673–1676; (c) Thomas, C. D.; McParland, J. P.; Hanson, P. R. Divalent and Multivalent Activation in Phosphate Triesters: A Versatile Method for the Synthesis of Advanced Polyol Synthons. *Eur. J. Org. Chem.* **2009**, 5487–5500.

[2] (a) Venukadasula, P. K. M.; Chegondi, R.; Maitra, S.; Hanson, P. R. A Concise, Phosphate-Mediated Approach to the Total Synthesis of (–)-Tetrahydrolipstatin. *Org. Lett.* **2010**, *12*, 1556–1559; (b) Hanson, P. R.; Chegondi, R.; Nguyen, J.; Thomas, C. D.; Waetzig, J. D.; Whitehead, A. Total Synthesis of Dolabelide C: A Phosphate-mediated Approach. *J. Org. Chem.* **2011**, *76*, 4358–4370; (c) Chegondi, R.; Tan, M. M. L.; Hanson, P. R. Phosphate Tether-mediated Approach to the Formal Total Synthesis of (–)-Salicylihalamides A and B. *J. Org. Chem.* **2011**, *76*, 3909–3916; (d) Jayasinghe, S.; Venukadasula, P. K. M.; Hanson, P. R. An Efficient, Modular Approach for the Synthesis of (+)-Strictifolione and a Related Natural Product. *Org. Lett.* **2014**, *16*, 122–125; (e) Chegondi, R.; Hanson, P. R. Synthetic Studies to Lyngbouilloside: A Phosphate Tether-mediated Synthesis of the Macrolactone Core. *Tetrahedron Lett.* **2015**, *56*, 3330–3333; (f) Bodugam, M.; Javed, S.; Ganguly, A.; Torres, J.; Hanson, P. R. A Pot-Economical Approach to the Total Synthesis of Sch-725674. *Org. Lett.* **2016**, *18*, 516–519; (g) Maitra, S.; Bodugam, M.; Javed, S.; Hanson, P. R. Synthesis of the C9–C25 Subunit of Spirastrellolide B. *Org. Lett.* **2016**, *Just Accepted.*

[3] (a) Venukadasula, P. K. M.; Chegondi, R.; Suryn, G. M.; Hanson, P. R. A Phosphate Tether-Mediated, One-Pot, Sequential Ring-Closing Metathesis/Cross-Metathesis/Chemoselective Hydrogenation Protocol. *Org. Lett.* **2012**, *14*, 2634–

2637; (b) Hanson, P. R.; Jayasinghe, S.; Maitra, S.; Ndi, C. N.; Chegondi, R. A Modular Phosphate Tether-mediated Divergent Strategy to Complex Polyols. *Beilstein J. Org. Chem.* **2014**, *10*, 2332–2337; (c) Javed, S.; Bodugam, M.; Torres, J.; Hanson, P. R. Modular Synthesis of Novel Macrocycles Bearing α,β-Unsaturated Chemotypes Through a Series of One-Pot, Sequential Protocols. *Chem. Eur. J.* **2016**, *22*, 6755–6758.

[4] Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. A General Model for Selectivity in Olefin Cross Metathesis. *J. Am. Chem. Soc.* **2003***, 125*, 11360–11370.

[5] For a few excellent reviews on aldol reactions and their applications in total syntheses, see: (a) Seijiro, H. Asymmetric Aldol Reactions in the Total Syntheses of Natural Products. *Stereosel. Synth. Drugs Nat. Prod.* **2016**, *1*, 215–247; (b) Ferreira, M. A. B.; Dias, L. C.; Leonarczyk, I. A.; Polo, E. C.; de Lucca, E. C. Exploring the Aldol Reaction in the Synthesis of Bioactive Compounds. *Curr. Org. Synth.* **2015**, *12*, 547–564; (c) Dibello, E.; Gamenara, D.; Seona, G. Organocatalysis in the Synthesis of Natural Products: Recent Developments in Aldol and Mannich Reactions and 1,4-Conjugated Additions. *Curr. Organocat.* **2015**, *2*, 124–149; (d) Kalesse, M.; Cordes, M.; Symkenberg, G.; Lu, H.-H. The Vinylogous Mukaiyama Aldol Reaction (VMAR) in Natural Product Synthesis. *Nat. Prod. Rep.* **2014**, *31*, 563–594; (e) Kalesse, M. Recent Advances in Vinylogous Aldol Reactions and Their Applications in the Syntheses of Natural Products. In *Natural Products Synthesis II*; Mulzer, J., Ed.; Springer: Berlin, Germany, 2005; pp.43–76.

[6] For a few excellent reviews on recent advances in asymmetric crotylation and allylation reactions, see: (a) Brown, H. C.; Ramachandran, P. V. Recent Advaces in the Boron Route to Asymmetric Synthesis. *Pure and Appl. CHem.* **1994**, *66*, 201–212; (b) Kennedy, J. W. J.; Hall, D. G. Recent Advances in Activation of Boron and Silicon Reagents for Stereocontrolled Allylation Reactions. *Angew. Chem. Int. Ed.* **2003**, *42*, 4732–4739; (c) Robertson, J.; Hall, M. J.; Green, S. P.

Stereospecificity in the Silicon Tethered α-(methyl)allylation of Aldehydes. *Org. Biomol. Chem.* **2003**, *1*, 3635–3638; (d) de Fatima, A.; Robello, L. G.; Pilli, R. A. *Quimica Nova* **2006**, *29*, 1009–1026; (e) Han, S. B.; Kim, I. S.; Krische, M. J. *Chem. Commun.* **2009**, *47*, 7278–7287; (f) Leighton, J. L. Powerful and Versatile Silicon Lewis Acids for Asymmetric Chemical Synthesis. *Aldrichim. Acta* **2010**, *43*, 3–12; (g) Moran, J.; Krische, M. J. Enantioselective Carbonyl Allylation and Crotylation from the Alcohol Oxidation Level via C-C Bond Forming Transfer Hydrogenation. *Asymm. Syn. II* **2012**, 187–196.

[7] For a few applicable reviews, see: (a) Keglevich, G.; Toeke, L; Ujszaszy, K.; Szoelloesy, A. Synthesis of Functionalized P-Heterocycles Including Phosphine-Borane Complexes. *Phosphorus, Sulfur and Silicon Relat. Elem.* **1996**, 457–460; (b) Ohff, M.; Holz, J.; Quirmbach, M.; Boerner, A. Borane Complexes of Trivalent Organophosphorus Compounds: Versatile Precursors for the Synthesis of Chiral Phosphine Ligands for Asymmetric Catalysis. *Synthesis* **1998**, *10*, 1391–1415; (c) Stankevic, M.; Pietrusiewicz, K. M. Synthesis and Reactivity of Phosphinous Acid-Borane Complexes. *Wiadomosci Chemiczne* **2006**, *60*, 323–343; (d) Bernoud, E.; Veillard, R.; Alayrac, C.; Gaumont, A.-C. Stoichiometric and Catalytic Synthesis of Alkynylphosphines. *Molecules* **2012**, *17*, 14573–14587.

[8] Heitsche, C. W.; Verkade, J. G. Phosphorus Complexes of Group III Acids. I. Boron Acids and 4-Methyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octaine. *Inorg. Chem.* **1962**, *2*, 392–398.

[9] Heitsche, C. W.; King, R. W.; Verkade, J. G. Phosphorus Complexes of Group III Acids. IV. $B^{11}$, $F^{19}$, $H^{1}$, and $P^{31}$ Nuclear Magnetic Resonance Studies of Boron Complexes of Polycyclic Phosphites. *Inorg. Chem.* **1964**, *3*, 884–889.

[10] Jin, Y.; Just, G. A Stereoselective Synthesis of Dinucleotide Boranophosphate, Using Chiral Indole-oxazaphosphorine Intermediates. *Tetrahedron Lett.* **1998**, *39*, 6429–6432.

[11] For excellent reviews on boranophosphate DNA mimics and boranophosphate nucleic acids, see: (a) Shaw, B. R.; Dobrikov, M.; Wang, X.; Wan, J.; He, K.; Lin, J.-L.; Li, P.; Rait, V.; Sergueeva, Z. A.; Sergueev, D. Reading, Writing, and Modulating Genetic Information with Boranophosphate Mimics of Nucleotides, DNA, and RNA. *Annals of the New York Academy of Sciences* **2003**, *1002*, 12–29; (b) Summers, J. S.; Shaw, B. R. Boranophosphates as Mimics of Natural Phosphodiesters in DNA. *Curr. Med. Chem.* **2001**, *8*, 1147–1155; (c) Shaw, B. R.; Sergueev, D.; He, K.; Porter, K.; Summers, J.; Sergueeva, Z.; Rait, V. Boranophosphate Backbone: A Mimic of Phosphodiesters, phosphorothioates, and Methylphosphonates. *Methods in Enzymology* **2000**, *313*, 226–257.

[12] Wada, T.; Maizuru, Y.; Shimizu, M.; Oka, N.; Saigo, K. Stereocontrolled Synthesis of Dithymidine Boranophosphates By an Oxazaphospholidine Method. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3111–3113.

[13] Oka, N.; Wada, T.; Saigo, K. Diastereocontrolled Synthesis of Dinucleoside Phosphorothioates Using a Novel Class of Activators, Dialkyl(cyanomethyl)ammonium Tetrafluoroborates. *J. Am. Chem. Soc.* **2002**, *124*, 4962–2963.

[14] Belabassi, Y.; Antczak, M. I.; Tellez, J.; Montchamp, J.-L. Borane Complexes of $H_3PO_2$ P(III) Tautomer: Useful Phosphinate Equivalents. *Tetrahedron* **2008**, *64*, 9181–9190.

[15] Deprele, S.; Montchamp, J.-L. A Novel and Convenient Preparation of Hypophosphite Ester. *J. Organomet. Chem.* **2002**, *643–644,* 154–163.

[16] Matsumura, F.; Oka, N.; Wada, T. Synthesis of Glycosyl Boranophosphates and Their Applications as Precursors of Glycosyl Phosphate Analogues. *Org. Lett.* **2008**, *10*, 1557–1560.

[17] Sekine, M.; Okimoto, K.; Yamada, K.; Hata, T. Silyl Phosphites. 15. Reactions of Silyl Phosphites with a-Halo Carbonyl Compounds. Elucidation of the Mechanism of the Perkow Reaction and Related Reactions with Confirmed Experiments. *J. Org. Chem.* **1981**, *46*, 2097–2107.

[18] Wada, T.; Shimizu, M.; Oka, N.; Saigo, K. A New Boranophosphorylation Reaction for the Synthesis of Deoxyribonucleoside Boranophosphates. *Tetrahedron Lett.* **2002**, *43*, 4137–4140.

[19] Schuman, M.; Trevitt, M.; Redd, A.; Gouverneur, V. Novel Synthesis of Borane Complexes of Cyclic Phosphanes Using Ruthenium-Catalyzed Olefin Metathesis. *Angew. Chem. Int. Ed.* **2000**, *39*, 2491–2493.

[20] Slinn, C. A.; Redgrave, A. J.; Hind, S. L.; Edlin, C.; Nolan, S.; Gouverneur, V. Synthesis of Unprotected and Borane-protected Cyclic Phosphines Using Ru- and Mo- based olefin metathesis catalysts. *Org. Biomol. Chem.* **2003**, *1,* 3820–3825.

[21] Timmer, M. S. M.; Ovaa, H.; Filippov, D. V.; van der Marel, G. A.; van Boom, J. H. Synthesis of Phosphorus Mono- and Bicycles by Catalytic Ring-Closing Metathesis. *Tetrahedron Lett.* **2001**, *42*, 8231–8233.

[22] Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. Increased Ring Closing Metathesis Activity of Ruthenium-based Olefin Metathesis Catalysts Coordinated with Imidazolin-2-ylidene Ligands. *Org. Lett.* **1999**, *1*, 953–956.

[23] Wu, X.; O'Brien, P.; Ellwood, S.; Secci, F.; Kelly, B. Synthesis of *P*-Stereogenic Phospholene Boranes via Asymmetric Deprotonation and Ring-Closing Metathesis. *Org. Lett.* **2013**, *15*, 192–195.

[24] Evans, D. A.; Yang, M. G.; Dart, M. J.; Duffy, J. L.; Kim, S. A. Enantioselective Deprotonation as Vehicle for the Asymmetric Synthesis of $C_2$-Symmetric *P*-Chiral Diphosphines. *J. Am. Chem. Soc.* **1995**, *117*, 9705–9076.

[25] *Jaspisamides and Kabiramides*: (a) Kobayashi, J.; Murata, O.; Shigemori, H. Sasaki, T. Jaspisamides A–C, New Cytotoxic Macrolides from the Okinawan Sponge *Jaspis* sp. *J. Nat. Prod.* **1993**, *56*, 787–791; (b) Matsunaga, S.; Fusetani, N.; Hashimoto, K. Kabiramide C, a Novel Antifungal Macrolide from Nudibranch Eggmasses. *J. Am. Chem. Soc.* **1986**, *108*, 849–850; (c) Klenchin, V. A.; Allingham, J. S.; King, R.; Tanaka, J.; Marriott, G.; Rayment, I. Trisoxazole Macrolide Toxins Mimic the Binding of Actin-capping Proteins to Actin. *Nat. Struct. Biol.* **2003**, *10*, 1058–1063; *Ulapualides:* (d) Roesener, J. A.; Scheuer, P. J.

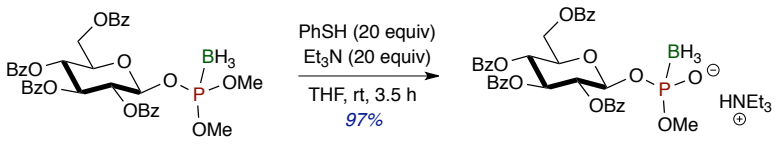
Ulapualide A and B, Extraordinary Antitumor Macrolides from Nudibranch Eggmasses. *J. Am. Chem. Soc.* **1986**, *108*, 846–847; *Halishigamides:* (*e*) Kobayashi, J.; Tsuda, M.; Fuse, H.; Sasaki, T.; Mikami, Y. Halishigamides A–D, New Cytotoxic Oxazole-Containing Metabolites from Okinawan Sponge *Halichondria* sp. *J. Nat. Prod.* **1997**, *60*, 150–154.

[26] Whitehead, A. Multivalent Activation in Temporary Phosphate Tethers: A New Tether for Small Molecule Synthesis. Ph.D. Thesis, University of Kansas, Lawrence, KS, May 2007.

[27] For resources on the proposed origins of this selectivity, along with illustrative models, see reference 1a.

[28] Williams, D. R.; Claeboe, C. D.; Liang, B.; Zorn, N.; Chow, N. S. C. A Bidirectional $S_E$' Strategy for 1,5-*syn* and 1.5-*anti* Stereocontrol Toward the Synthesis of Complex Polyols. *Org. Lett.* **2012**, *14*, 3866–3869.

[29] *C*-Functionalization of phosphite borane triesters has received little attention outside deprotection-oxidation strategies to provide either H-phosphonates or boranophosphates. In this regard, it was reported that the addition of thiophenol to a glucose-dimethylphosphite borane, in the presence of triethylamine, at room temperature, provided the corresponding phosphinous acid salt via nucleophilic de-methylation (*vide infra*). This salt was later oxidized to the H-phosphonate in a demethylation-oxidation protocol. For more information, see: Sato, K.; Oka, N.; Fujita, S.; Matsumura, F.; Wada, T. 1,2-*Trans*-Selective Synthesis of Glycosyl Boranophosphates and Their Utility as Building Blocks for the Synthesis of Phosphodiester-Linked Disaccharides. *J. Org. Chem.* **2010***, 75*, 2147–2156.




[30] For a representative example, see: Uziel, J.; Darcel, C.; Moulin, D.; Baudin, C.; Juge, S. Chemo-, Regio-, and Stereoselective Conversion of *P*-Chirogenic

Phosphorus Borane Complexes into their P=O or P=S Derivatives. *Tetrahedron: Asymmetry* **2001**, *12*, 1441–1449.

[31] All X-ray crystallographic data has been submitted to the Cambridge Crystallographic Data Centre, and the structures for this work were assigned the following deposition numbers: ($R_P$,*R*,*R*)-**3.9.5** [1484372] and ($S_P$,*S*,*S*)-**3.9.4** [1484373].

# Chapter 4

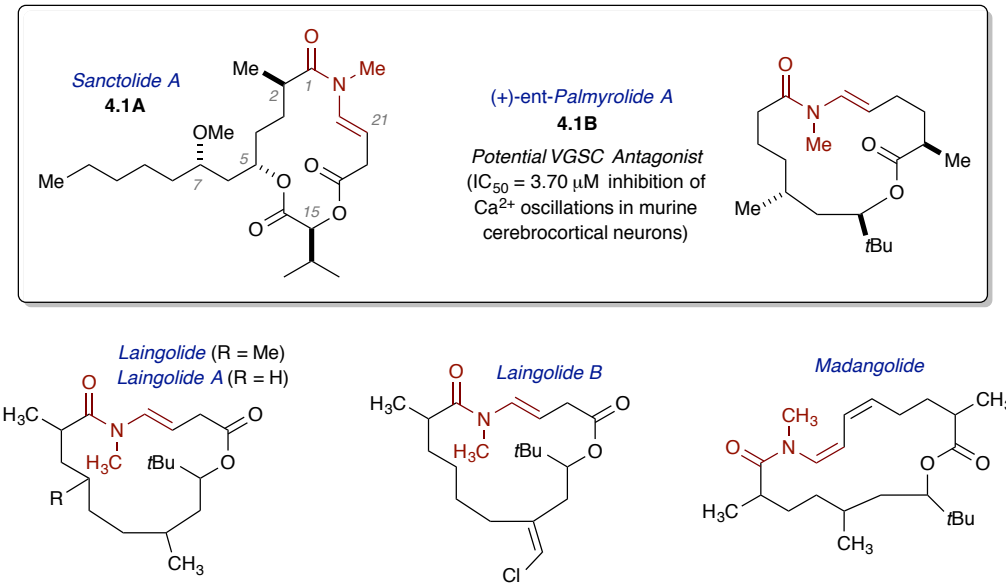
*Phosphate Tether Methods Toward the*

*Modular Total Synthesis of 2*S-*Sanctolide A*

## 4.1 Introduction

Sanctolide A (**4.1A**) was isolated from a moderatively cytotoxic cell extract of cyanobacterium *Oscillatoria sancta* (SAG 74.79) by Orjala and coworkers in 2012 (Figure 4.1).[1] The 14-membered marine macrolide was found to possess a central 1,3-*anti*-diol subunit, a lipophilic pentyl side-chain, and both a diester linkage and *N*-methyl enamide motif within the macrocyclic portion of the molecule. The polyketide/non-ribosomal peptide hybrid **4.1A** is part of a small class of cyclic *N*-methyl enamide-containing natural products, including the laingolides,[2] madangolide,[2a] and neuroprotective (+)-*ent*-palmyrolide A (**4.1B**).[3] Though secondary cyclic enamides are well-represented in the literature (including >200 known cyclopeptide alkaloids with a range of biological activities),[4] the cyclic tertiary enamide (in particular, the *N*-methyl enamide) is relatively rare, and biological evaluation of this class is somewhat limited—outside that of palmyrolide A. For these reasons, this class of compounds are interesting

**Figure 4.1** *Sanctolide A and other cyclic* N*-methyl enamide-containing natural products.*

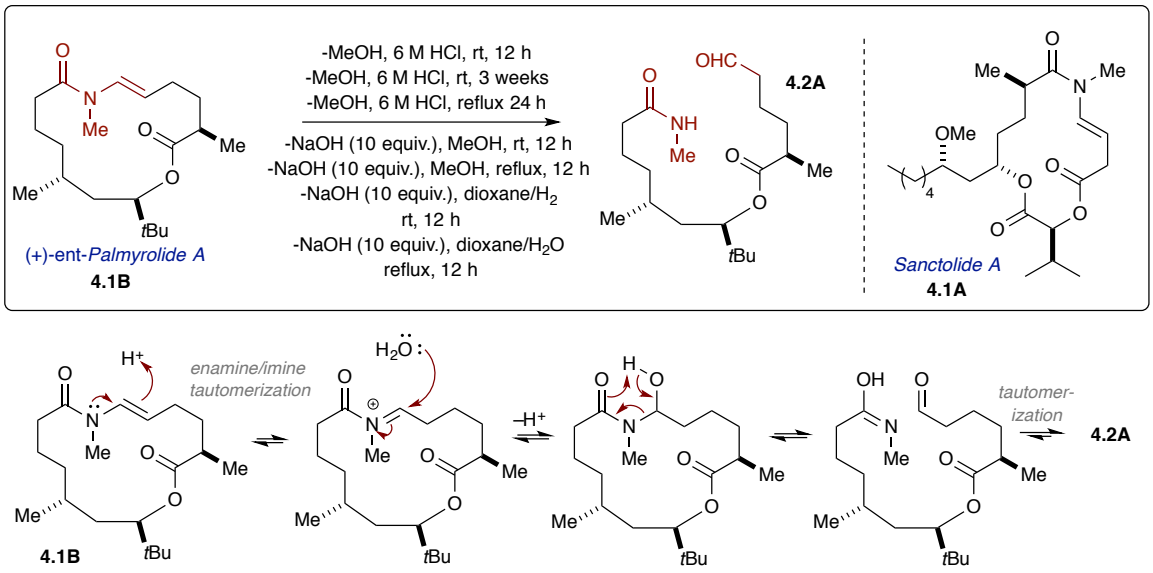


synthetic targets—particularly for the purpose of the generation of libraries of analogs for biological screening.

Sanctolide A (**4.1A**) was surprisingly labile, when compared to the remarkable stability of palmyrolide A (**4.1B**),[3] and was found to undergo enamide hydrolysis in the presence of water under both acidic and neutral conditions. The authors proposed a mechanism for enamide hydrolysis of **4.1A** carried out under neutral conditions based upon the previously proposed mechanism for the acid-catalyzed hydrolysis of **4.1B** (Figure 4.2).[3] Pereira and coworkers propose that a reversible, acid-catalyzed enamide tautomerization would provide an intermediate iminium, to which $H_2O$ could add to form a transient hemiaminal. Collapse of the hemiaminal, followed by amide tautomerization, then affords the corresponding ring-opened product (**4.2A**) containing both a secondary *N*-methyl amide and an aldehyde.[3] While this mechanism seems feasible for hydrolysis of the *N*-methyl enamide moiety in strongly acidic conditions (6 M HCl), the exact mechanism of the enamide hydrolysis of **4.1A** under neutral conditions remains unclear, as the first proposed step (enamide/imine tautomerization) would be difficult without facilitating acid and this particular mechanism would not necessarily explain the significant differences in the stability of **4.1A** as compared to **4.1B**. Thus, the generation of larger quantities of **4.1A**, as well as a variety of analogs, may aid to elucidate the mechanism of enamide hydrolysis and pin-point origins of this hydrolytic instability. In addition, as **4.1A** was completely hydrolyzed to the acyclic product after stirring in the presence of water for 48 hours, Orjala and coworkers hypothesized that the biological activity observed for **4.1A** (moderate cytotoxicity in brine shrimp toxicity assay, 23.5

μM) was most likely attributed to degradation product—since hydrolysis was likely to occur under the conditions necessary for biological assay. Thus, synthetic strategies that would allow for the facile formation of analogs of sanctolide A—

**Figure 4.2** *Proposed mechanism for acid-catalyzed enamide hydrolysis of* **4.1B**.

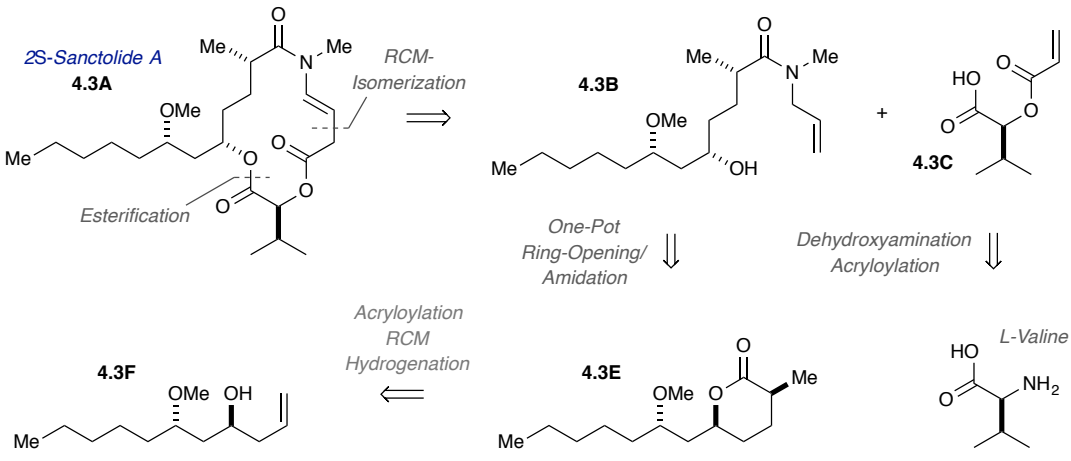



particularly those with enhanced hydrolytic stability—could serve as useful tools to facilitate a comprehensive understanding of the biological potential of this relatively rare class of PK-NRP hybrids. In this regard, we herein report our synthetic efforts toward the total synthesis of C2-epimer of sanctolide A—with potential applications to the total synthesis of the title natural product (**4.1A**). Investigations focus on the development of phosphate tether-mediated one-pot sequential protocols that would allow for a streamlined synthesis of the C1–C12-fragment of C2-*epi*-sanctolide A, with the potential to provide the wherewithal to generate libraries of analogs in a facile manner.

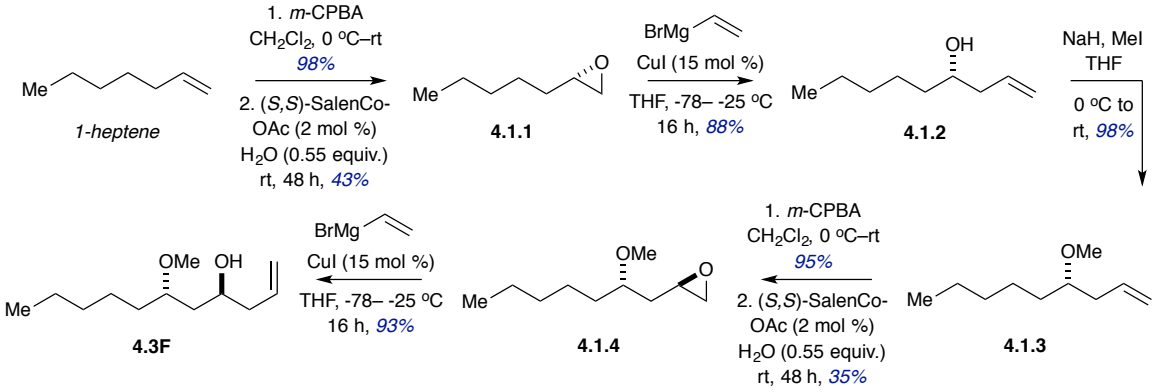
*4.1.1 Total Synthesis of 2*S*-Sanctolide A*

In 2014, Brimble and coworkers reported the total synthesis of 2*S*-sanctolide A (**4.3A**) via similar strategies involving a key RCM-olefin isomerization macrocyclization initially developed for the total synthesis of palmyrolide A (**4.1B**) (Figure 4.3).[5] It should be noted that the authors did not intend to synthesize the C2-epimer of sanctolide A—as the exact stereochemistry of the C2-methyl group was undefined in the isolation report. However, this synthetic strategy did serve to define the C2-stereochemistry of the natural product. Retrosynthetic analysis of 2*S*-sanctolide A (**4.3A**) showed that the natural product could be synthesized via an RCM-olefin isomerization protocol of the ester derived from the coupling of alcohol **4.3B** and carboxylic acid **4.3C** (obtained in 2 steps from L-valine). Correspondingly, **4.3B** could be generated from 1,3-*anti*-diol-containing lactone **4.3E**, which could be formed from olefinic alcohol **4.3F** via methacryloylation, RCM, and stereoselective hydrogenation of the intermediate α,β-unsaturated lactone.

**Figure 4.3** *Retrosynthetic analysis of 2*S*-sanctolide A.*



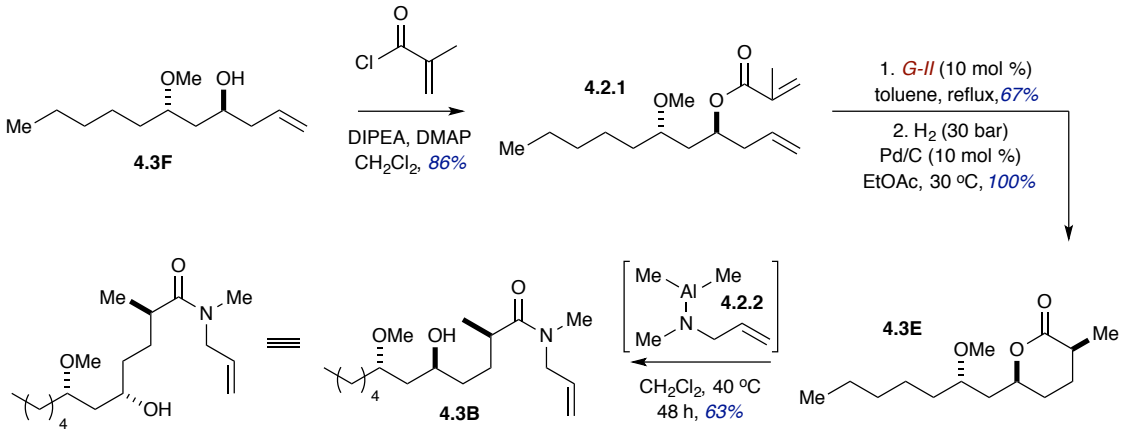
Synthesis commenced with the epoxidation of hept-1-ene, which provided the corresponding epoxides (not shown) in 98% yield as a racemate; hydrolytic kinetic resolution (HKR) of the racemic mixture with Jacobsen's (*R,R*)-salenCo$^{III}$-OAc catalyst[6] furnished known epoxide **4.1.1**[7] in 43% (Scheme 4.1). Epoxide ring opening with vinyl-magnesium bromide, in the presence of catalytic copper(I) iodide, afforded homo-allylic alcohol **4.1.2**, and subsequent methylation with sodium hydride and methyl iodide provided **4.1.3** in excellent overall yield. Similarly, olefin **4.1.3** was expoxidized with *m*-CPBA (95% yield, 1:1 mix of enantiomers) and exposed to HKR conditions to afford 1,3-*anti*-diol product **4.1.4** in 35% yield as a single diastereomer. Finally, epoxide ring opening of **4.1.4**, again with vinyl-magnesium bromide/catalytic CuI, then generated olefinic alcohol **4.3F** in excellent yield.




**Scheme 4.1** *Synthesis of intermediate **4.3F**.*

Intermediate **4.3F** was acylated with methacryloyl chloride, in the presence of diispropyl(ethyl)amine (DIPEA), to afford diene **4.2.1** in 86% yield (Scheme 4.2). Treatment of **4.2.1** with Grubbs' second-generation catalyst[8] (G-II, [(ImesH$_2$)(PCy$_3$)(Cl)$_2$Ru=CHPh], 10 mol %), followed by stereoselective hydrogenation

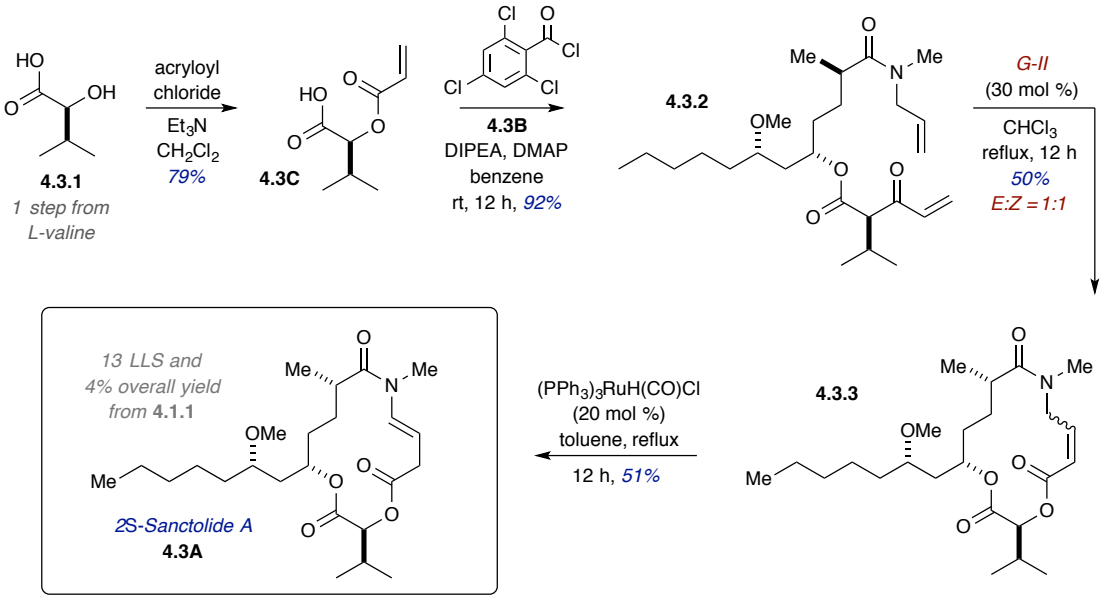
with $H_2$ (30 bar) and Pd/C (10 mol %), generated the 3,6-*syn*-diastereomer of lactone **4.3E** in good overall yield. The authors note that the stereoselectivity of this hydrogenation is likely the result of the C6-substituent, which blocks the top *Si*-face approach of the palladium catalyst and allows for preferential addition of "$H_2$" to the bottom *Re*-face of the reactive olefin. One-pot lactone ring-opening/amidation of **4.3E** with *in-situ*-generated dimethylaluminum amide **4.2.2**[9] furnished amide **4.3B** in 63% yield.




**Scheme 4.2** *Synthesis of intermediate **4.3B**.*

Next, acid **4.3C** was generated via coupling of β-hydroxyisovaleric acid **4.3.1** (commercially available or 1 step from L-valine)[10] with acryloyl chloride (Scheme 4.3). Subsequent esterification of **4.3C** with the *in-situ*-generated mixed anhydride of 2,4,6-trichlorobenzoyl chloride and intermediate **4.3B** provided RCM-precursor **4.3.2** in 92% yield. Exposure of **4.3B** to G-II (30 mol %), in refluxing chloroform, furnished macrocyclic tertiary amide **4.3.3** in 50% yield, as a proposed 1:1 mixture of *E*- and *Z*-isomers. Final Ru-hydride-mediated olefin isomerization of amide **4.3.3** (diastereomeric mixture) afforded *E*-configured *N*-methyl-enamide 2*S*-sanctolide A (**4.3A**) in 50% yield.

The authors concluded that the final product (**4.3A**) was the C2-epimer of the desired natural product (sanctolide A, **4.1A**) by comparative analysis of optical rotation and $^{1}$H NMR spectra. Overall, the synthetic strategy provided **4.3A** in 13 longest linear steps (LLS) and 4% overall yield from known epoxide **4.1.1** (Scheme 4.1) and successfully laid the ground-work for future syntheses of sanctolide A (**4.1A**).



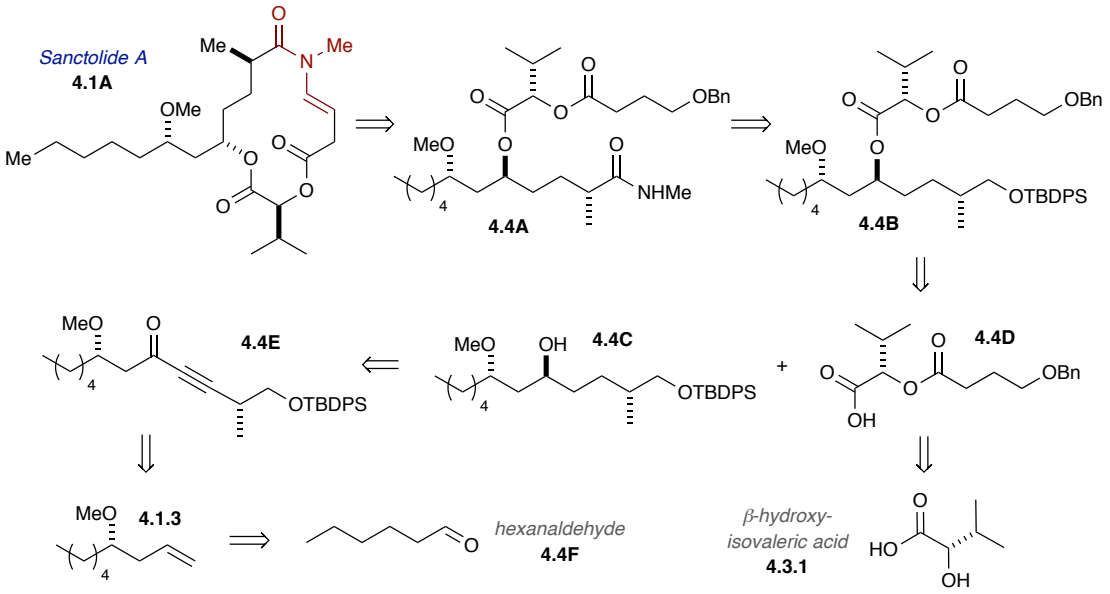

**Scheme 4.3** *RCM-isomerization macrocyclization end-game strategy to 2S-sanctolide A.*

*4.1.2 Total Synthesis of Sanctolide A*

Recently, in 2015, Yadav, Suresh, and Srihari published the first and only total synthesis of sanctolide A (**4.1A**).[11] The authors envisioned that **4.1A** could be generated via a late-stage oxidation-condensation cyclization strategy from amide **4.4A**, which could be derived in 4 steps from **4.4B** (Figure 4.4). Correspondingly, diester **4.4B** could be provided by the coupling of alcohol **4.4C** with acid **4.4D** (obtained in 3 steps from commercially available 2-β-hydroxyisovaleric acid). 1,3-*Anti*-diol-containing **4.4C** could

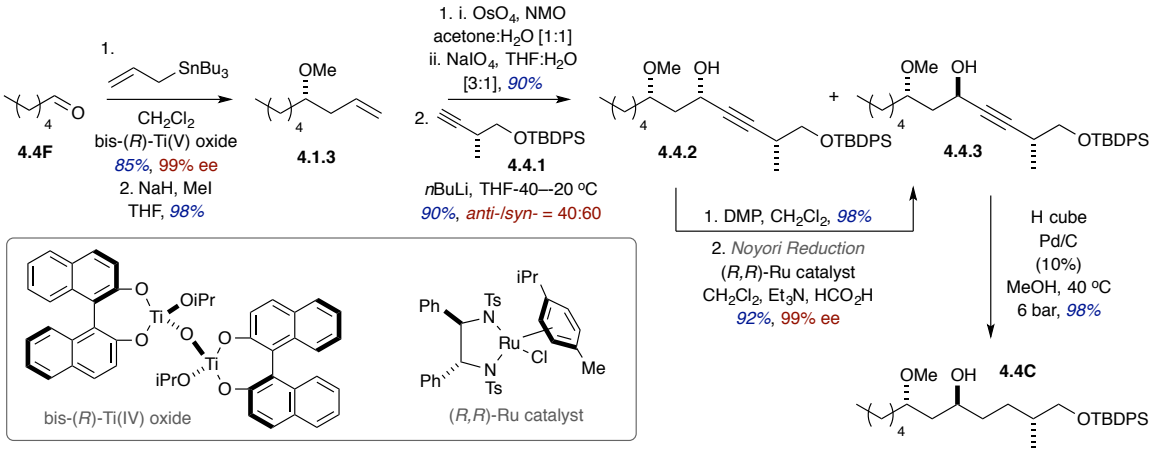
be generated via Noyori reduction,[12] followed by alkyne reduction, of β-methoxy-ketone **4.4E**, which could be derived in 5 steps from hexanaldehyde **4.4F**.

**Figure 4.4** *Retrosynthetic analysis to sanctolide A.*




Following this synthetic plan, the authors first set their sights on the generation of alcohol **4.4C**. Asymmetric allylation of hexanaldehyde (**4.4F**) with allyltributyl tin and bis-(*R*)-Ti(IV) oxide catalyst provided the corresponding homoallylic alcohol (not shown) in 85% yield and 99% enantiomeric excess; this intermediate was smoothly methylated to afford **4.1.3** (Scheme 4.4). Upjohn dihydroxylation[13] of **4.1.3** and oxidative cleavage of the resultant diol furnished a terminal aldehyde that was coupled with lithiated alkyne **4.4.1** to generate propargyl 1,3-skipped diol products *syn*-**4.4.2** and the desired *anti*-**4.4.3** in 90% yield, but as an unfavorable diastereomeric ratio (*syn*:*anti* = 60:40). However, oxidation of *syn*-**4.4.2** with Dess-Martin periodinane (DMP),[14] followed by diastereoselective Noyori reduction of the resultant ketone, furnished desired alcohol *anti*-**4.4.3** in good overall yield and selectivity. Finally, alkyne reduction of **4.4.3**

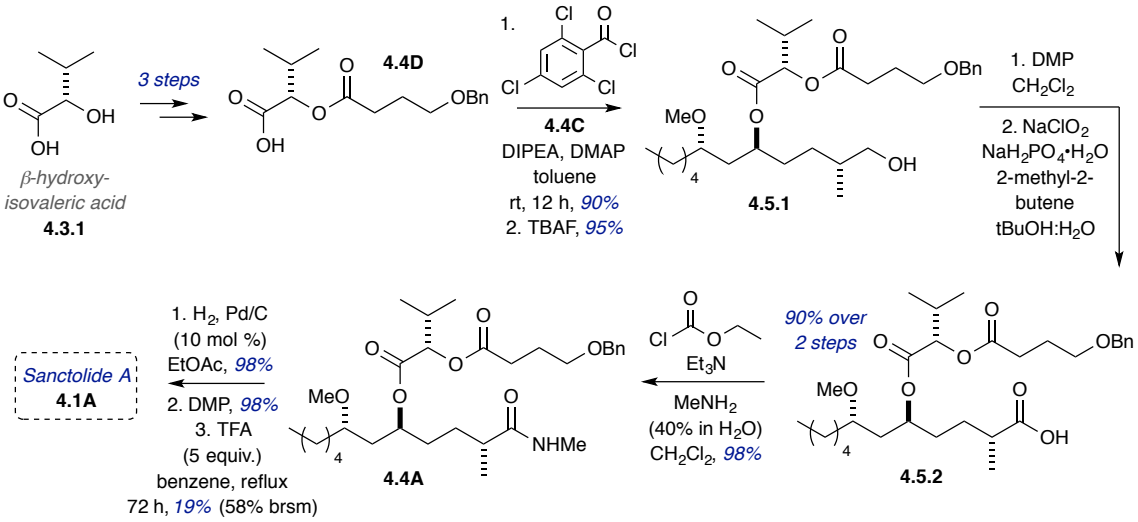
with an H-cube equipped with a Pd/C (10%) cartridge, under pressure (6 bar), afforded intermediate alcohol **4.4C** in 98% yield.




**Scheme 4.4** *Stereoselective synthesis of coupling partner* **4.4C**.

Alcohol **4.4C** was coupled with acid **4.4D**, obtained in 3 steps from **4.3.1**, via conditions developed by Yamaguchi and coworkers (2,4,6-trichlorobenzoylchloride, DIPEA, DMAP),[15] followed by silyl-deprotection with TBAF, to provide **4.5.1** in excellent overall yield (Scheme 4.5). DMP oxidation of the primary alcohol in **4.5.1**, followed by Pinnick oxidation[16] of the resultant aldehyde, furnished the corresponding acid (**4.5.2**) in 90% yield over 2 steps. Subsequent one-pot sequential mixed anhydride formation and amidation (with aqueous methyl amine) afforded **4.4A** in near quantitative yield. Intermediate **4.4A** was treated with $H_2$, in the presence of Pd/C (10 mol %) in EtOAc, to unveal a primary alcohol, which was oxidized with DMP and stirred in refluxing benzene, in the presence of catalytic trifluoroacetic acid (TFA), for 3 days, to generate sanctolide A, albeit in low yield (19%, 58% based on recovered starting material). As the characteristic data obtained for the product of the synthesis was in good

agreement with that reported in the isolation paper,[1] this synthesis confirmed the absolute configuration of the natural product 2*R*-sanctolide A.

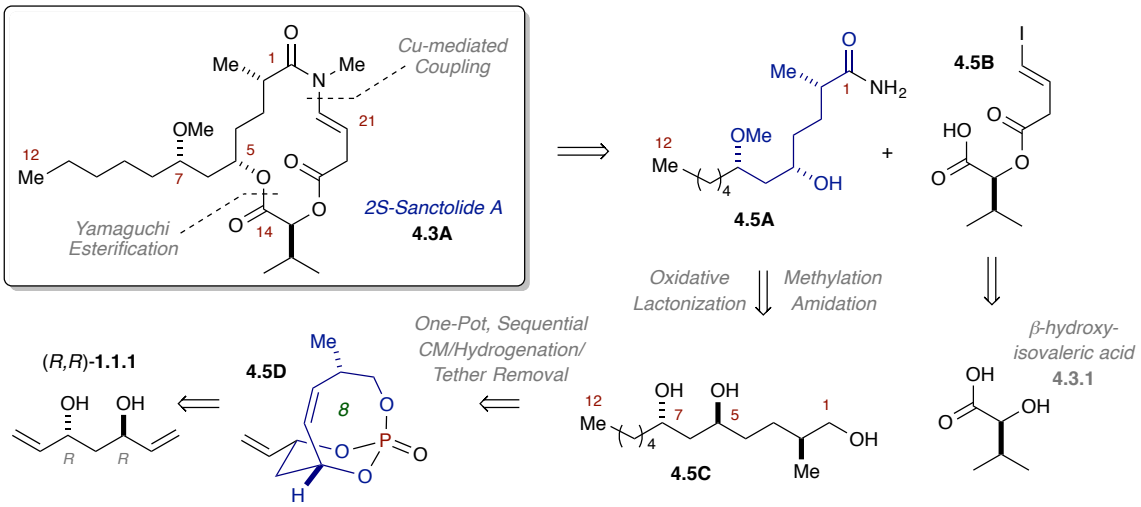



**Scheme 4.5** *Esterification and macrocyclization to sanctolide A.*

## 4.2 Results and Discussion

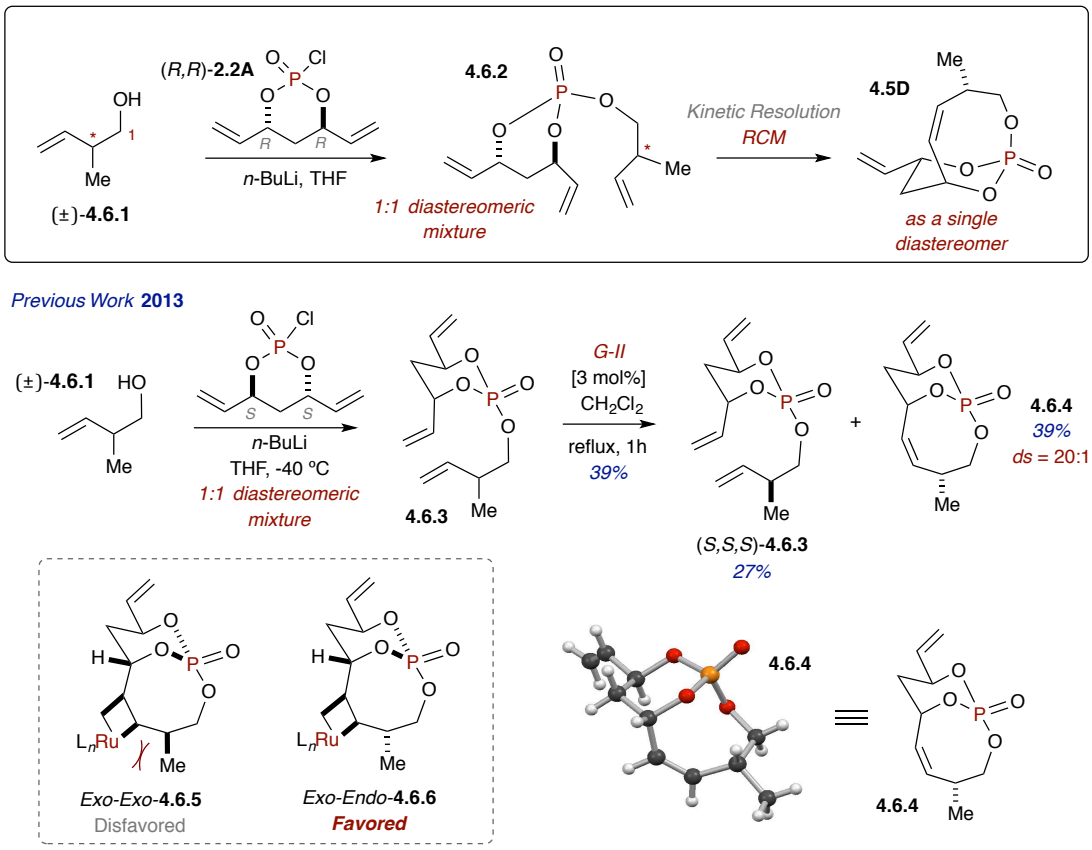
Our retrosynthetic plan involved the formation of 2*S*-sanctolide A (**4.3A**) by the Yamaguchi esterification[15a] and late-stage macrocyclization copper-mediated coupling of amide alcohol **4.5A** with vinyl-idodide-containing acid **4.5B** that was inspired by the impressive synthetic efforts of Maio and coworkers to the total synthesis of palmyrolide A (**4.1B**) (Figures 4.1 and 4.5).[15b] We envisioned that acid **4.5B** could be derived from 2-β-hydroxyisovaleric acid and that amide alcohol **4.5A** could be generated from triol **4.5C**. Correspondingly, triol **4.5C** could be furnished from bicyclo[5.4.1]phosphate **4.5D** through a phosphate tether-mediated, one-pot sequential cross metathesis/global hydrogenation/tether removal strategy, similar to those previously reported by our group (See Chapter 1 of this thesis).[17]

**Figure 4.5** *Retrosynthetic analysis to 2S-sanctolide A.*



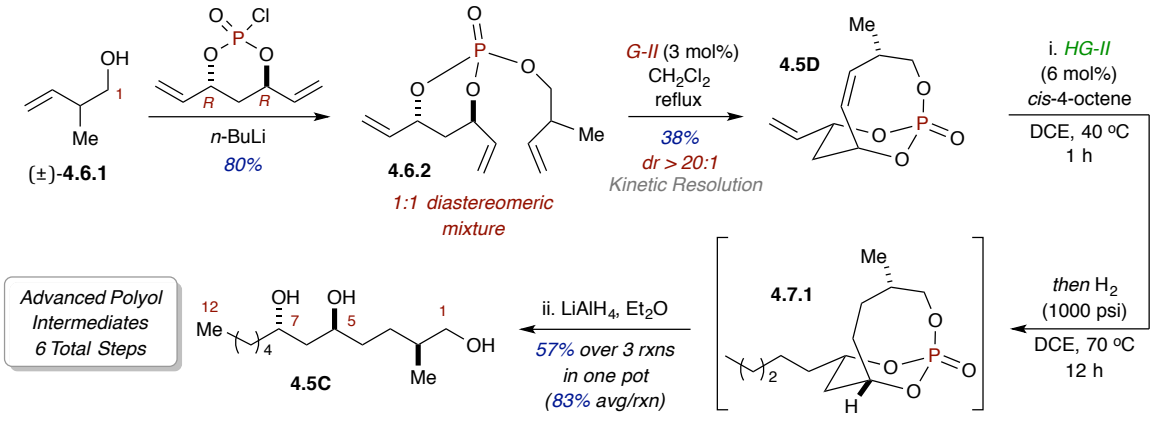

Based upon previous reports from our laboratory, we proposed that bicyclo[5.3.1]phosphate **4.5D** could be generated via a phosphate tether-mediated double diastereotopic group differentiation of trienes **4.6.2**, as was shown for the corresponding enantiomer of **4.5D** (bicyclo[5.3.1]phosphate **4.6.4**, Scheme 4.6).[1819] In 2013, our group published a detailed study on the effects of stereochemical complexity, ring size, and olefin substitution on phosphate tether-mediated ring-closing metathesis which included the synthesis of bicyclo[5.3.1]phosphate **4.6.4**. Chiral, racemic olefinic alcohol **4.6.1** was coupled with monochlorophosphate (*S,S*)-**2.2A** to provide trienes **4.6.3** as a 1:1 mixture of diastereomers. This mixture was treated with G-II (3 mol %), in refluxing methylene chloride, to provide bicyclo[5.3.1]phosphate **4.6.4** in 39% yield as a single diastereomer (along with diastereomerically enriched, unreacted starting material). The absolute configuration was confirmed by X-ray crystallographic analysis of **4.6.4**, and a mechanistic rationale based upon proposed structures of intermediate Ru-metallocyclobutanes was developed to explain the observed diastereoselectivity. Because

of the concave nature of the bicyclic phosphate, we proposed that only those metallocyclobutanes that formed on the *exo*-face of the forming olefin would be energetically feasible. When the allylic methyl substituent is also on the *exo*-face of the bicyclic phosphate (as in *exo-exo*-**4.6.5**), an unfavorable 1,2-steric interaction between the methyl group and the Ru-metallocyclobutane would exist, increasing the energy of this intermediate and impeding the RCM from taking place. When the allylic methyl substituent is on the opposite *endo*-face of the bicyclic phosphate (as in *exo-endo*-**4.6.6**), the unfavorable 1,2-steric interaction is avoided, and the reaction proceeds.



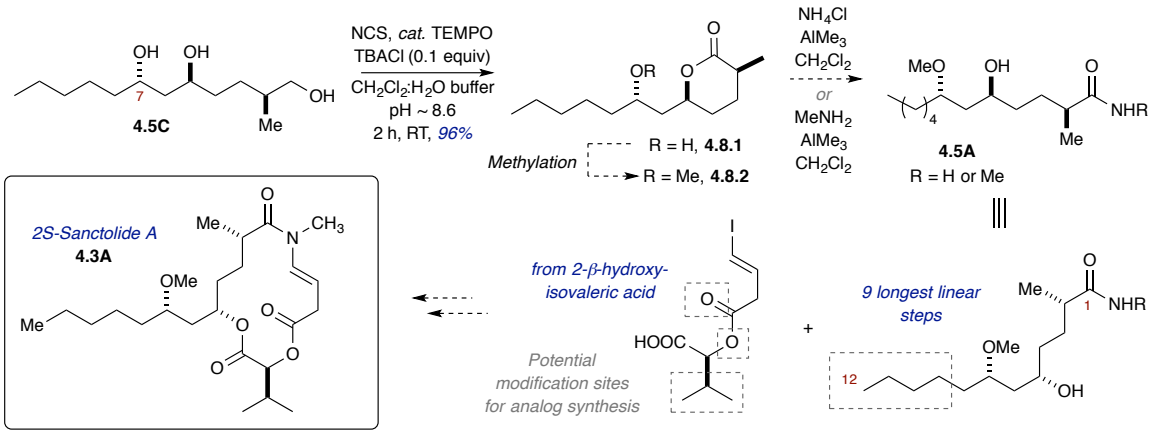

**Scheme 4.6** *Plans for a kinetic resolution/double diastereotopic differentiation and mechanistic rationale for diastereoselectivity based upon previous work.*

Thus, lithiated chiral, racemic homoallylic alcohol **4.6.1** was coupled with (*R,R*)-**2.2A**, in THF, to provide trienes **4.6.2** in 80% yield (Scheme 4.7). Trienes **4.6.2** were exposed to RCM conditions (G-II, refluxing methylene chloride) to furnish the corresponding bicyclo[5.3.1]phosphate **4.5D** as a single diastereomer in 38% yield. Then, a one-pot, sequential cross metathesis of **4.5D** with *cis*-4-octene, in the presence of Hoveyda-Grubbs second-generation catalyst[20] (HG-II, 6 mol %), followed by global hydrogenation of both *endo*- and *exo*-cyclic olefins catalyzed by residual HG-II (resulting in the transient formation of bicylic phosphate **4.7.1**)[21] and subsequent tether removal, generates triol **4.5C** in 57% yield over 3 reactions in one pot (83% average per reaction). This strategy allows for the formation of advanced polyol intermediates (similar to **4.5C**) in 6 total steps (or "pots") with the modularity to incorporate a variety of diverse side-chains (through cross-metathesis) for the facile synthesis of libraries of analogs from a common intermediate—a capability that is noticeably absent from the previously described synthesis of **4.1A** and its C2-epimer.




**Scheme 4.7** *Phosphate tether-mediated kinetic resolution and one-pot sequential CM/H$_2$/Tether removal to* **4.5C**.

With triol **4.5C** in hand, we turned our efforts toward identifying a protocol that would allow for the selective methylation of the C7-hydroxyl group and oxidation of the C1-alcohol en route to amide **4.5A**. It was found that exposure of **4.5C** to *N*-chlorosuccinimide (NCS), in the presence of catalytic TEMPO (10 mol %) and facilitating tetrabutylammonium chloride, provided lactone **4.8.1** in 96% yield, with no observable over oxidation of C7 (Scheme 4.8).[22] In this way, the oxidation state of C1 is successfully achieved, and the C5-hydroxyl group is protected to allow for selective methylation of the C7-hydroxyl group. Methylation of **4.8.1**, followed by tandem ring-opening/amide formation via protocols similar to those previously described (*vide supra*),[5] would allow for the formation of amide **4.5A** in 9 longest-linear pots and facilitate the synthesis of 2*S*-sanctolide A (**4.3A**), as well as provide precedence for other phosphate tether strategies to the synthesis of the natural product (**4.1A**) and its analogs.

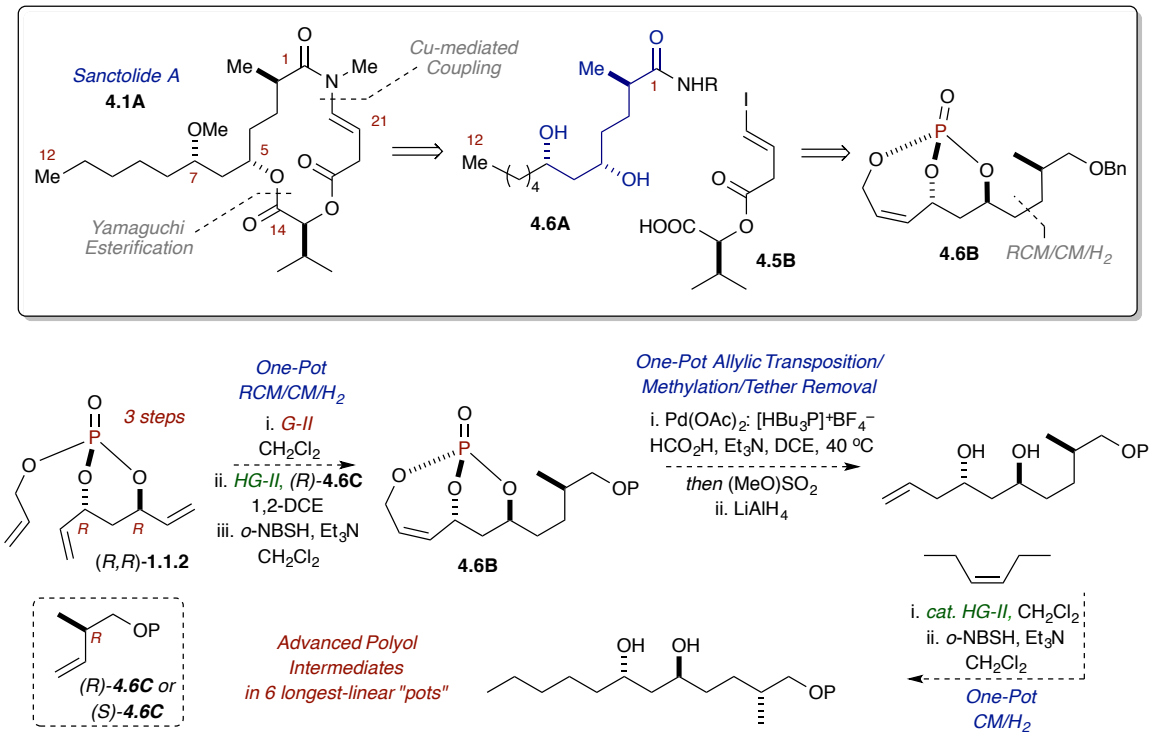



**Scheme 4.8** *Oxidative lactonization and future plans toward amide* **4.5A**.

## 4.3 Conclusions and Future Goals

In conclusion, efforts toward the synthesis of 2*S*-sanctolide A—in particular, the C1–C12 amide fragment—are described. Our strategy involves the use of a RCM that serves as a kinetic resolution to afford an 8-membered bicyclo[5.3.1]phosphate via a double diastereotopic group differentiation. In addition, a phosphate tether-mediated one-pot sequential CM-global hydrogenation-tether removal protocol was developed to afford advanced polyol intermediates in 6 total pots. Oxidative lactonization of the resultant triol **4.5C** allows for a selective protection of the C5-hydroxyl group and allows the means to methylate the C7-hydroxyl group selectively. Future efforts will involve identification of a mild methylating technique that minimizes C2-epimerization and the application of a ring-opening/amide formation strategy, in a manner similar to that reported by Brimble and coworkers en route to **4.1B** (*vide supra*).[5] In addition, efforts will focus on the development of phosphate tether-mediated one-pot, sequential processes for the synthesis of 2*R*-sanctolide A and its analogs. We propose that the natural product could be generated via the coupling of amide **4.6A** (the C2-epimer of **4.5A**) and acid **4.5B**, where **4.6A** is derived from RCM/CM/hydrogenation product bicylo[4.3.1]phosphate **4.6B** (Figure 4.6). Two, one-pot sequential processes involving allylic transposition/methylation/tether removal and cross-metathesis/hydrogenation would then provide the analogous C2-epimer of triol **4.5D**, again in 6 longest-linear pots, and allow for the synthesis of **4.1A** via conserved late-stage transformations from the 2*S*-sanctolide strategy.

**Figure 4.6** *Proposed phosphate-tether mediated, one-pot sequential protocols toward the synthesis of 2R-sanctolide A.*



## 4.4 References Cited


[1] Kang, H. S; Krunic, A.; Orjala, J. Sanctolide A, a 14-Membered PK-NRP Hybrid Macrolide from the Cultured Cyanobacterium *Oscillatoria sancta* (SAG 74.79). *Tetrahedron Lett.* **2012**, *53*, 3563–3567.

[2] (a) Klein, D.; Braekman, J. C.; Daloze, D.; Hoffmann, L.; Castillo, G.; Demoulin, V. Madangolide and Laingolide A, Two Novel Macrolides from *Lyngbya bouillonii* (Cyanobacteria). *J. Nat. Prod*. **1999**, *62*, 934−936; (b) Klein, D.; Braekman, J.-C.; Daloze, D. Laingolide, a Novel 15-Membered Macrolide from *Lyngbya bouillonii* (cyanophyceae). *Tetrahedron Lett.* **1996**, *37*, 7519−7520; (c) Matthew, S.; Salvador, L. A.; Schupp, P. J.; Paul, V. J.; Luesch, H. Cytotoxic Halogenated Macrolides and Modified Peptides from the Apratoxin-Producing Cyanobacterium *Lyngbya bouillonii* from Guam. *J. Nat. Prod*. **2010**, *73*, 1544−1552.

[3] Pereira, A. R.; Cao, Z.; Engene, N.; Soria-Mercado, I. E.; Murray, T. F.; Gerwick, W. H. Palmyrolide A, an Unusually Stabilized Neuroactive Macrolide from Palmyra Atoll Cyanobacteria. *Org. Lett.* **2010**, *12*, 4490–4493.

[4] (a) Kuranaga, T.; Sesoko, Y.; Inoue, M. Cu-mediated Enamide Formation in the Total Synthesis of Complex Peptide Natural Products. *Nat. Prod. Rep.* **2014**, *31*, 514–532, and references cited therein; (b) El-Seedi, H. R.; Zahra, M. H.; Goransson, U.; Verpoorte, R. Cyclopeptide Alkaloids. *Phytochem. Rev.* **2007**, *6*, 143–165.

[5] Wadsworth, A. D.; Furkert, D. P.; Brimble, M. A. Total Synthesis of the Macrocyclic *N*-Methyl Enamides Palmyrolide A and 2*S*-Sanctolide A. *J. Org. Chem.* **2014**, *79*, 11179–11193.

[6] Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. Asymmetric Catalysis with Water: Efficient Kinetic Resolution of Terminal Epoxides by Means of Catalytic Hydrolysis. *Science* **1997***, 277*, 936–938.

[7] Haase, B.; Schneider, M. P. Enzyme-Assisted Synthesis of Enantiomerically Pure δ-Lactones. *Tetrahedron: Asymmetry* **1993**, *4*, 1017−1026.

[8] Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. Synthesis and Activity of a New Generation of Ruthenium-Based Olefin Metathesis Catalysts Coordinated with 1,3-Dimesityl-4,5-dihydroimidazol-2-ylidene Ligands. *Org. Lett.* **1999**, *1*, 953–956.

[9] Kim, S.; Wu, J. Y.; Zhang, Z.; Tang, W.; Doss, G. A.; Dean, B. J.; DiNinno, F.; Hammond, M. L. Estrogen Receptor Ligands. 12. Synthesis of the Major Metabolites of an ERα-Selective, Dihydrobenzoxathiin Antagonist for Osteoporosis. *Org. Lett.* **2005**, *7*, 411–414.

[10] Müller, J.; Feifel, S. C.; Schmiederer, T.; Zocher, R.; Süssmuth, R. D. In vitro Synthesis of New Cyclodepsipeptides of the PF1022-Type: Probing the α-D-Hydroxy Acid Tolerance of PF1022 Synthetase. *Chem. Bio. Chem.* **2009**, *10*, 323−328.

[11] Yadav, J. S.; Surresh, B.; Srihari, P. Stereoselective Total Synthesis of the Marine Macrolide Sanctolide A. *Eur. J. Org. Chem.* **2015**, *26*, 5856–5863.

[12] (a) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. Asymmetric Transfer Hydrogenation of Imines. *J. Am. Chem. Soc*. **1996**, *118*, 4916–4917; (b) Denmark, S. E.; Yang, S.-M. Total Synthesis of (+)-Brasilenyne. Application of an Intramolecular Silicon-Assisted Cross-Coupling Reaction. *J. Am. Chem. Soc.* **2004**, *126*, 12432–12440; (c) Raghavan, S.; Kumar, V. V. A Stereoselective Synthesis of the C9–C19 Subunit of (+)-Peloruside A. *Org. Biomol. Chem*. **2013**, *11*, 2847–2858; (d) Arai, N.; Satosh, H.; Utsumi, N.; Murata, K.; Tsutsumi, K.; Ohkuma, T. Asymmetric Reduction of Diynones and the Total Synthesis of (S)-Panaxjapyne A. *Org. Lett*. **2013**, *15*, 3030–3033.

[13] Van Rheenen, V; Kelly, R. C.; Cha, D. Y. An Improved Catalytic $OsO_4$ Oxidation of Olefins to *cis*-1,2-Glycols Using Tertiary Amine Oxides as the Oxidant. *Tetrahedron Lett.* **1976**, *17,* 1973–1976.

[14] Paterson, I.; Anderson, E. A.; Dalby, S. M.; Lim, J. H.; Genovino, J.; Maltas, P.; Moessner, C. Total Synthesis of Spirastrellolide A Methyl Ester—Part 1: Synthesis of an Advanced C17–C40 Bis-spiroacetal Subunit. *Angew. Chem. Int. Ed.* **2008**, *47*, 3021–3025.

[15] (a) Inanga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. A Rapid Esterification by Means of Mixed Anhydride and Its Application to Large-ring Lactonization. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993; (b) Tello-Aburto, R.; Johnson, E. M.; Valdez, K. C.; Maio, W. A. Asymmetric Total Synthesis and Absolute Stereochemistry of the Neuroactive Marine Macrolide Palmyrolide A. *Org. Lett.* **2012**, *14*, 2150–2153.

[16] (a) Lindgren, B. O.; Nilsson, T. Preparation of Carboxylic Acids from Aldehydes (Including Hydroxylated Benzaldehydes) by Oxidation with Chlorite. *Acta Chemica Scandinavica* **1973**, *27*, 888–890; (b) Bal, B. S.; Childers, W. E.; Pinnick, H. W. Oxidation of α,β-Unsaturated Aldehydes. *Tetrahedron* **1981**, *37*, 2091–2096.

[17] (a) Venukadasula, P. K. M.; Chegondi, R.; Suryn, G.; Hanson, P. R. A Phosphate Tether-Mediated, One-pot, Sequential Ring-Closing Metathesis/Cross-Metathesis/Chemoselective Hydrogenation Protocol. *Org. Lett.* **2012**, *14*, 2634–2637; (b) Jayasinghe, S.; Venukadasula, P. K. M.; Hanson, P. R. An Efficient, Modular Approach for the Synthesis of (+)-Strictifolione and a Related Natural Product. *Org. Lett.* **2014**, *16*, 122–125; (c) Bodugam, M.; Javed, S.; Ganguly, A.; Torres, J.; Hanson, P. R. A Pot-Economical Approach to the Total Synthesis of Sch-725674. *Org. Lett.* **2016**, *18*, 516–519; (d) Hanson, P. R.; Jayasinghe, S.; Maitra, S.; Ndi, C. N.; Chegondi, R. A Modular Phosphate Tether-mediated Divergent Strategy to Complex Polyols. *Beilstein J. Org. Chem.* **2014**, *10*, 2332–2337; (e) Javed, S.; Bodugam, M.; Torres, J.; Ganguly, A.; Hanson, P. R. Modular Synthesis of Novel Macrocycles Bearing α,β-Unsaturated Chemotypes via a Series of One-Pot, Sequential Protocols. *Chem. Eur. J.* **2016**, *22*, 6755–6758.

[18] Chegondi, R.; Maitra, S.; Markley, J. L.; Hanson, P. R. Phosphate-Tether-Mediated Ring-Closing Metathesis for the Preparation of Complex 1,3-anti-Diol-Containing Subunits. *Chem. Eur. J.* **2013**, *19*, 8088–8093.

[19] Maitra, S. Phosphate Tether-Mediated Metathesis Studies and Application Towards Natural Product Synthesis. Ph.D. Thesis, University of Kansas, Lawrence, KS, June 2016.

[20] (a) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J., Jr.; Hoveyda, A. H. A Recyclable Ru-Based Metathesis Catalyst. *J. Am. Chem. Soc*. **1999**, *121*, 791−799; (b) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. Efficient and Recyclable Monomeric and Dendritic Ru-Based Metathesis Catalysts. *J. Am. Chem. Soc*. **2000**, *122*, 8168−8179.

[21] Louie, J.; Bielawski, C. W.; Grubbs, R. H. Tandem Catalysis: The Sequential Mediation of Olefin Metathesis, Hydrogenation, and Hydrogen Transfer with Single-Component Ru Complexes. *J. Am. Chem. Soc.*, **2001**, *123*, pp 11312–11313.

[22] The chemoselective oxidation of primary alcohols in the presence of secondary alcohols using NCS, TEMPO, and facilitating TBACl was first reported by Einhorn and coworkers in 1996. See: Einhorn, J.; Einhorn, C.; Ratajczak, F.; Pierre, J.-L. Efficient and Highly Selective Oxidation of Primary Alcohols to Aldehydes by *N*-Chlorosuccinimide Mediated by Oxoammonium Salts. *J. Org. Chem.* **1996**, *61*, 7452–7454.

# Chapter 5

## Supporting Information for Chapters 2–4:

*Methods, Experimental Data, and NMR Spectra*

## 5.1 Supporting Information for Chapter 2

*Phosphate Tether-Mediated Ring-Closing Metathesis Studies to Bicyclo[n.3.1]phosphates: Extended Investigations on the Effect of Ring Size, Stereochemical Complexity, and Olefin Substitution*

# *Table of Contents*

## Chapter 5, Section 1: Supporting Information for Chapter 2

*Phosphate Tether-Mediated Ring-Closing Metathesis Studies to Bicyclo[n.3.1]phosphates: Extended Investigations on the Effect of Ring Size, Stereochemical Complexity, and Olefin Substitution*

### 5.1.1 General Methods

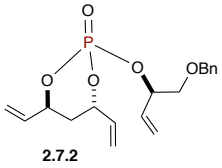
All reactions were carried out in oven- or flame-dried glassware under argon atmosphere using standard gas-tight syringes, cannulae, and septa. Stirring was achieved with oven-dried magnetic stir bars. Toluene, THF and $CH_2Cl_2$ were purified by passage through a purification system (Solv-Tek) employing activated $Al_2O_3$ (Grubbs, R. H.; Rosen. R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520). $Et_3N$ was purified by passage over basic alumina and stored over KOH. Butyllithium was purchased from Aldrich and titrated prior to use. All olefin metathesis catalysts were acquired from Materia and used without further purification. Flash column chromatography was performed with Sorbent Technologies (30930M-25, Silica Gel 60A, 40-63 mm) and thin layer chromatography was performed on silica gel $60F_{254}$ plates (EM-5717, Merck). Deuterated solvents were purchased from Cambridge Isotope laboratories. $^{1}H$, $^{13}C$, DEPT, COSY, HSQC, HMBC and NOESY NMR spectra were recorded in $CDCl_3$ (unless otherwise mentioned) on a Bruker DRX-500 spectrometer operating at 500 MHz, and 125 MHz, respectively, calibrated to the solvent peak, and utilized to unambiguously assign proton and carbon signals. $^{31}P$ NMR spectra was recorded on Bruker DRX-400 spectrometer operating at 162 MHz. High-resolution mass spectrometry (HRMS) was recorded on a LCT Premier Spectrometer (Micromass UK Limited) operating on ESI (MeOH). Observed rotations at 589 nm, were measured using AUTOPOL IV Model automatic polarimeter. IR was recorded on Shimadzu FTIR-8400S instrument.

### 5.1.2 Experimental Section

**General procedure for Triene generation (1):** To a solution of alcohol (1.1 equiv) in THF (0.2 M), at -40 ºC under argon, was added *n*-BuLi (2.5 M in hexanes, 1 equiv), dropwise. The mixture was allowed to stir for 5 minutes, at which point a solution of phosphate monochloride (1.2 equiv) in THF (1 mL) was slowly added to the reaction vessel via cannulation. The mixture stirred at –40 ºC for 2 hours (monitored by TLC) and was quenched with aqueous $NH_4Cl$ (sat.). The biphasic solution was separated, and the aqueous layer was extracted EtOAc (3 x 5 mL). The combined organic layers were washed with brine, dried ($Na_2SO_4$), and concentrated under reduced pressure. Purification via flash chromatography (silica, Hexanes:EtOAc eluent) provided triene-containing monocyclic phosphate triester product.

**General procedure for RCM to provide bicyclo[n.3.1]phosphates (2):** To a flask containing monocyclic phosphate triester (1 equiv.) in $CH_2Cl_2$ (dry, degassed, 0.001 M), equipped with an argon inlet and reflux condenser, was added *p*-benzoquinone (10 mol %). Then, G-I or G-II catalyst [see reaction schemes] was added to the reaction [portion-wise in 1 mol % quantities over the allotted reaction time], and the reaction mixture was heated to reflux. Upon completion (monitored by TLC), the reaction was cooled to room temperature and concentrated under reduced pressure. Purification via flash chromatography (silica, Hexanes:EtOAc eluent) provided the corresponding bicyclic phosphate.

**(4*S*,6*S*)-2-(((*R*)-1-(benzyloxy)but-3-en-2-yl)oxy)-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide (2.7.2):**




2.7.2

Following General Procedure 1, monochlorophosphate (*S,S*)-**2.2A**[1] (0.102 g, 0.489 mmol) and alcohol (*R*)-**2.7.1**[2] (0.0872 g, 0.489 mmol) were converted into triene **2.7.2** (0.106 g, 0.301 mmol, 62% yield) which was isolated as a pale yellow oil.

**FTIR** (neat): 2924, 2856, 1454, 1281, 1009, 741 $cm^{-1}$.

**Optical Rotation**: $[\alpha]_D$ = +47.6 (*c* = 0.38, $CHCl_3$).

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.37–7.26 (m, 5H), 6.05 (ddd, J = 16.9, 10.6, 6.0 Hz, 1H), 5.99–5.85 (m, 1H), 5.94 (ddd, *J* = 17.1, 10.6, 6.5 Hz, 1H), 5.46 (d, *J* = 6.7 Hz, 1H), 5.42 (d, *J* = 6.8 Hz, 1H), 5.37 (d, *J* = 17.1 Hz, 1H), 5.32 (d, *J* = 4.6 Hz, 1H), 5.29 (d, *J* = 4.6 Hz, 1H), 5.26 (d, *J* = 10.6 Hz, 1H), 5.11–4.95 (m, 3H), 4.62 (d, *J* = 12.1 Hz, 1H), 4.57 (d, *J* = 12.1 Hz, 1H), 3.71–3.61 (m, 2H), 2.12 (ddddd, J = 16.4, 14.8, 10.8, 5.2, 1.7 Hz, 2H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 137.9 (s), 135.2 (d, $J_{CP}$ = 3.3 Hz), 135.0 (s), 135.0 (s), 133.8 (d, $J_{CP}$ = 4.1 Hz), 128.3 (s), 127.6 (s), 118.7 (s), 117.8 (s), 117.4 (s), 78.2 (d, $J_{CP}$ = 5.6 Hz), 77.9 (d, $J_{CP}$ = 6.7 Hz), 76.0 (d, $J_{CP}$ = 6.1 Hz), 73.2 (s), 72.2 (d, $J_{CP}$ = 5.9 Hz), 35.2 (d, $J_{CP}$ = 7.7 Hz).

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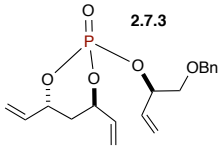
[1] Whitehead, A.; McReynolds, M. D.; Moore, J. D.; Hanson, P. R. Multivalent Activation in Temporary Phosphate Tethers: A New Tether for Small Molecule Synthesis. *Org. Lett.* **2005**, *7*, 3375–3378.
[2] Davoille, R. J.; Rutherford, D. T.; Christie, S. D. R. Homologation of Allylic Alcohols. An Approach to Cyclic and Acyclic Polyoxygenated Compounds. *Tetrahedron Lett.* **2000**, *41*, 1255–1259.

**$^{31}$P NMR (162 MHz, $CDCl_3$)** δ -8.23.

**HRMS:** cald. for $[C_{18}H_{23}O_5P]_2Na$ $(2M+Na)^+$ 723.2464; found 723.2456 (TOF MS ES+).

**(4*R*,6*R*)-2-(((*R*)-1-(benzyloxy)but-3-en-2-yl)oxy)-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide (2.7.3):**




Following General Procedure 1, monochlorophosphate (*R,R*)-**2.2A** (0.105 g, 0.503 mmol) and alcohol (*R*)-**2.7.1** (0.0900 g, 0.503 mmol) were converted into triene **2.7.3** (0.082 g, 0.234 mmol, 46% yield) which was isolated as a colorless oil.

**FTIR** (neat): 3085, 2922, 1427, 1285, 1007, 739 $cm^{-1}$.

**Optical Rotation**: $[\alpha]_D$ = -53.9 (*c* = 1.7, $CHCl_3$).

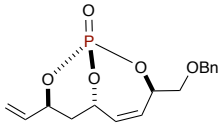
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.36–7.27 (m, 5H), 6.09 (dddd, *J* = 17.1, 10.6, 6.4, 0.8 Hz, 1H), 5.91 (ddd, *J* = 17.0, 10.7, 6.2 Hz, 1H), 5.82 (dddd, *J* = 17.3, 10.6, 5.2, 1.7 Hz, 1H), 5.46 (ddd, *J* = 17.2, 1.2, 1.2 Hz, 1H), 5.38 (ddd, *J* = 4.7, 1.0, 1.0 Hz, 1H), 5.34 (ddd, *J* = 4.7, 1.1, 1.1 Hz, 1H), 5.31 (d, *J* = 10.9 Hz, 1H), 5.28 (ddd, *J* = 10.8, 1.0, 1.0 Hz, 1H), 5.23 (ddd, *J* = 10.7, 1.0, 1.0 Hz, 1H), 5.10 – 4.97 (m, 3H), 4.61 (d, *J* = 11.9 Hz, 1H), 4.54 (d, *J* = 11.9 Hz, 1H), 3.64–3.61 (m, 2H), 2.12 (dddd, *J* = 14.5, 8.0, 4.9, 1.6 Hz, 1H), 2.03 (dddd, *J* = 14.8, 5.5, 3.7, 1.8 Hz, 1H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 137.7 (s), 135.2 (s), 135.2 (d, $J_{CP}$ = 4.8 Hz), 133.4 (d, $J_{CP}$ = 4.0 Hz), 128.4 (s), 127.8 (s), 127.7 (s), 118.6 (s), 118.0 (s), 117.1 (s), 78.2 (d, $J_{CP}$ = 6.8 Hz), 77.8 (d, $J_{CP}$ = 5.5 Hz), 75.9 (d, $J_{CP}$ = 6.1 Hz), 73.2 (s), 72.3 (d, $J_{CP}$ = 5.8 Hz), 35.3 (d, $J_{CP}$ = 7.7 Hz).

**$^{31}$P NMR (162 MHz, $CDCl_3$)** δ -8.37.

**HRMS:** cald. for $[C_{18}H_{23}O_5P]_2Na$ $(2M+Na)^+$ 723.2464; found 723.2400 (TOF MS ES+).

**(1*S*,3*R*,6*S*,8*S*)-3-((benzyloxy)methyl)-8-vinyl-2,9,10-trioxa-1-phosphabicyclo[4.3.1]-dec-4-ene 1-oxide (*trans*-2.7.4):**




*trans*-**2.7.4**

Following General Procedure 2, triene **2.7.2** (20.0 mg, 0.0571 mmol) was exposed to G-II catalyst (6 mol %, added portion-wise over 6 h) in refluxing $CH_2Cl_2$ to provide the corresponding bicyclic phosphate *trans*-**2.7.4** (10.0 mg, 0.0310 mmol, 54% yield, 72% based upon recovered starting material) as a white, crystalline solid, which was recrystallized (EtOAc:Hexanes) to afford X-ray quality crystals for X-ray crystallographic analysis.[3] In addition to the title product, unreacted triene **2.7.2** (4.9 mg, 0.014 mmol) was recovered during purification of the crude reaction mixture.

**FTIR** (neat): 2924, 2866, 1454, 1300, 1086, 741 $cm^{-1}$.

**Optical Rotation**: $[\alpha]_D$ = +146. (*c* = 0.49, $CHCl_3$).

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.42–7.28 (m, 5H), 6.02 (ddd, *J* = 12.3, 5.9, 1.8 Hz, 1H), 5.86 (dddd, *J* = 17.1, 10.5, 5.2, 1.7 Hz, 1H), 5.66 (dd, *J* = 12.5, 4.4 Hz, 1H), 5.44 (d, *J* = 17.1 Hz, 1H), 5.28 (d, *J* = 10.6 Hz, 1H), 5.15 (ddd, *J* = 24.6, 4.2, 4.2 Hz, 1H), 5.02 (dd, *J* = 11.6, 4.6 Hz, 1H), 4.92 (ddd, *J* = 29.2, 12.5, 6.0 Hz, 1H), 4.71 (d, *J* = 12.0 Hz, 1H),

[3] All X-ray crystallographic data has been submitted to the Cambridge Crystallographic Data Centre, and the structure for *trans*-**2.7.4** was assigned the following deposition number: 905668.

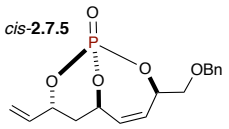
4.60 (d, $J$ = 12.0 Hz, 1H), 4.06 (dd, $J$ = 10.3, 7.0 Hz, 1H), 3.84 (dd, $J$ = 10.3, 5.9 Hz, 1H), 2.26 (ddd, $J$ = 14.5, 11.9, 6.1 Hz, 1H), 1.79 (d, $J$ = 14.6 Hz, 1H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 137.6 (s), 134.7 (d, $J_{CP}$ = 10.4 Hz), 129.8 (s), 128.9 (s), 128.4 (s), 127.9 (s), 127.8 (s), 117.5 (s), 76.3 (d, $J_{CP}$ = 7.8 Hz), 75.9 (d, $J_{CP}$ = 6.6 Hz), 75.8 (d, $J_{CP}$ = 6.8 Hz), 73.7 (s), 72.0 (s), 34.4 (d, $J_{CP}$ = 5.7 Hz).

**$^{31}$P NMR (162 MHz, $CDCl_3$)** δ -7.86.

**HRMS:** cald. for $[C_{16}H_{19}O_5P]_2Na$ $(2M+Na)^+$ 667.1838; found 667.1848 (TOF MS ES+).

**(1*R*,3*R*,6*R*,8*R*)-3-((benzyloxy)methyl)-8-vinyl-2,9,10-trioxa-1-phosphabicyclo[4.3.1]-dec-4-ene 1-oxide (*cis*-2.7.5):**




Following General Procedure 2, triene **2.7.3** (35.0 mg, 0.100 mmol) was exposed to G-II catalyst (3 mol %) in refluxing $CH_2Cl_2$ to provide the corresponding bicyclic phosphate *cis*-**2.7.5** (24.6 mg, 0.0763 mmol, 76% yield) as a pale yellow oil.

**FTIR** (neat): 2924, 2854, 1454, 1298, 968, 764 $cm^{-1}$.

**Optical Rotation**: $[\alpha]_D$ = -17.6 ($c$ = 0.42, $CHCl_3$).

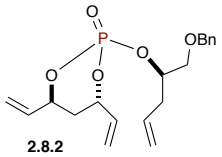
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.41–7.28 (m, 5H), 6.04 (ddd, $J$ = 11.9, 2.5, 2.5 Hz, 1H), 5.84 (ddd, $J$ = 10.6, 5.9, 2.0 Hz, 1H), 5.61 (ddd, $J$ = 11.9, 3.9, 2.4 Hz, 1H), 5.43 (d, $J$ = 17.2 Hz, 1H), 5.33–5.27 (m, 1H), 5.27 (d, $J$ = 10.6 Hz, 1H), 5.27–5.16 (m, 1H), 5.04 (dd, $J$ = 11.9, 5.3 Hz, 1H), 4.64 (dd, $J$ = 12.1 Hz, 1H), 4.59 (dd, $J$ = 12.1 Hz, 1H), 3.72 (ddd, $J$ = 10.2, 5.0, 1.0 Hz, 1H), 3.63 (dd, $J$ = 10.3, 6.0 Hz, 1H), 2.23 (ddd, $J$ = 14.7, 12.1, 6.2 Hz, 1H), 1.80 (dd, $J$ = 14.4, 2.0 Hz, 1H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 137.5 (s), 134.7 (d, $J_{CP}$ = 10.4 Hz), 130.1 (s), 129.4 (s), 128.5 (s), 127.9 (s), 127.7 (s), 117.4 (s), 77.1 (s), 76.2 (d, $J_{CP}$ = 6.0 Hz), 73.5 (s), 72.2 (d, $J_{CP}$ = 5.9 Hz), 71.2 (d, $J_{CP}$ = 12.1 Hz), 34.9 (d, $J_{CP}$ = 5.9 Hz).

**$^{31}$P NMR (162 MHz, $CDCl_3$)** δ -5.74.

**HRMS:** cald. for $[C_{16}H_{19}O_5P]_2Na$ $(2M+Na)^+$ 667.1838; found 667.1835 (TOF MS ES+).

**(4*S*,6*S*)-2-(((*R*)-1-(benzyloxy)pent-4-en-2-yl)oxy)-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide (2.8.2):**




2.8.2

Following General Procedure 1, monochlorophosphate (*S,S*)-**2.2A** (0.102 g, 0.489 mmol) and alcohol (*R*)-**2.8.1**[4] (0.0970 g, 0.489 mmol) were converted into triene **2.8.2** (0.116 g, 0.318 mmol, 65% yield) which was isolated as a colorless oil.

**FTIR** (neat): 2924, 2858, 1454, 1283, 1007, 739 $cm^{-1}$.

**Optical Rotation**: $[\alpha]_D$ = +37.9 (*c* = 0.33, $CHCl_3$).

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.36–7.27 (m, 5H), 6.04 (ddd, *J* = 17.2, 10.7, 6.1 Hz, 1H), 5.90 (dddd, *J* = 17.3, 10.6, 5.2, 1.7 Hz, 1H), 5.80 (ddt, *J* = 17.2, 10.1, 7.1 Hz, 1H), 5.45 (ddd, *J* = 17.2, 1.3, 1.3 Hz, 1H), 5.35 (ddd, *J* = 17.2, 1.3, 1.3 Hz, 1H), 5.30 (ddd, *J* = 10.6, 1.2, 1.2 Hz, 1H), 5.23 (ddd, *J* = 10.6, 1.2, 1.2 Hz, 1H), 5.15 (dd, *J* = 17.1, 1.7 Hz, 1H), 5.12–5.08 (m, 1H), 5.08–4.96 (m, 2H), 4.71–4.62 (m, 1H), 4.59 (d, *J* = 12.0 Hz,

[4] Hashimura, K. Tomita, S.; Hiroya, K.; Ogasawara, K. A Stereocontrolled Route to Both Enantiomers of the Necine Base Dihydroxyheliotridane via Intramolecular 1,3-Dipolar Addition Using the Same Chiral Precursor. *J. Chem. Soc., Chem. Commun.* **1995**, 2291–2292.

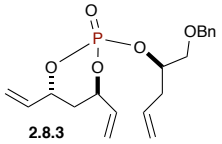
1H), 4.54 (d, $J$ = 12.0 Hz, 1H), 3.70–3.59 (m, 2H), 2.62–2.45 (m, 2H), 2.18–2.02 (m, 2H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 138.0 (s), 135.2 (d, $J_{CP}$ = 3.2 Hz), 135.1 (s), 135.0 (s), 133.0 (s), 128.3 (s), 127.6 (s), 118.4 (s), 117.8 (s), 117.3 (s), 77.9 (d, $J_{CP}$ = 6.8 Hz), 77.2 (s), 75.9 (d, $J_{CP}$ = 6.1 Hz), 73.22 (s), 71.2 (d, $J_{CP}$ = 4.4 Hz), 36.7 (d, $J_{CP}$ = 4.9 Hz), 35.2 (d, $J_{CP}$ = 7.6 Hz).

**$^{31}$P NMR (162 MHz, $CDCl_3$)** δ -8.26.

**HRMS:** cald. for $[C_{19}H_{25}O_5P]_2Na$ $(2M+Na)^+$ 751.2777; found 751.2770 (TOF MS ES+).

**(4*R*,6*R*)-2-(((*R*)-1-(benzyloxy)but-3-en-2-yl)oxy)-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide (2.8.3):**




2.8.3

Following General Procedure 1, monochlorophosphate (*R,R*)-**2.2A** (0.105 g, 0.503 mmol) and alcohol (*R*)-**2.8.1** (0.0970 g, 0.503 mmol) were converted into triene **2.8.3** (0.102 g, 0.280 mmol, 56% yield) which was isolated as a colorless oil.

**FTIR** (neat): 2924, 2862, 1454, 1283, 1004, 740 $cm^{-1}$.

**Optical Rotation**: $[\alpha]_D$ = -57.6 ($c$ = 0.46, $CHCl_3$).

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.38–7.26 (m, 5H), 6.08 (ddd, $J$ = 17.0, 10.6, 6.2 Hz, 1H), 5.87–5.74 (m, 2H), 5.36 (d, $J$ = 11.0 Hz, 1H), 5.32 (d, $J$ = 11.0 Hz, 1H), 5.28 (d, $J$ = 10.6 Hz, 1H), 5.22 (d, $J$ = 10.6 Hz, 1H), 5.13 (dd, $J$ = 17.03, 1.6 Hz, 1H), 5.10 (d, $J$ = 9.8, 1H), 5.07–4.96 (m, 2H), 4.68–4.60 (m, 1H), 4.58 (d, $J$ = 11.8 Hz, 1H), 4.50 (d, $J$ = 11.8

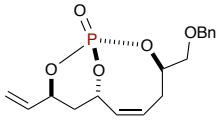
Hz, 1H), 3.65–3.55 (m, 2H), 2.60–2.47 (m, 2H), 2.09 (ddd, $J$ = 8.1, 4.9, 1.6 Hz, 1H), 2.01 (dddd, $J$ = 14.7, 5.4, 3.9, 1.9 Hz, 1H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 137.8 (s), 135.2 (d, $J_{CP}$ = 6.4 Hz), 135.2 (d, $J_{CP}$ = 1.0 Hz), 132.7 (s), 128.3 (s), 127.7 (s), 127.7 (s), 118.4 (s), 117.9 (s), 117.0 (s), 78.1 (d, $J_{CP}$ = 6.8 Hz), 77.0 (d, $J_{CP}$ = 6.3 Hz), 75.7 (d, $J_{CP}$ = 6.0 Hz), 73.2 (s), 71.3 (d, $J_{CP}$ = 4.9 Hz), 36.7 (d, $J_{CP}$ = 4.3 Hz), 35.3 (d, $J_{CP}$ = 7.6 Hz).

**$^{31}$P NMR (162 MHz, $CDCl_3$)** δ -8.19.

**HRMS:** cald. for $[C_{19}H_{25}O_5P]_2Na$ $(2M+Na)^+$ 751.2777; found 751.2760 (TOF MS ES+).

**(1*S*,3*R*,7*S*,9*S*,*Z*)-3-((benzyloxy)methyl)-9-vinyl-2,10,11-trioxa-1-phosphabicyclo[5.3.1]undec-5-ene 1-oxide (*trans*-2.8.4):**




*trans*-**2.8.4**

Following General Procedure 2, triene **2.8.2** (33.6 mg, 0.0923 mmol) was exposed to G-II catalyst (3 mol %) in refluxing $CH_2Cl_2$ to provide the corresponding bicyclic phosphate *trans*-**2.8.4** (22.0 mg, 0.0654 mmol, 71% yield) as a pale yellow oil.

**FTIR** (neat): 2926, 2854, 1454, 1283, 1020, 756 $cm^{-1}$.

**Optical Rotation**: $[\alpha]_D$ = +61.8 ($c$ = 0.45, $CHCl_3$).

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.38–7.28 (m, 5H), 5.89–5.80 (m, 2H), 5.53 (d, $J$ = 11.8 Hz, 1H), 5.41 (ddd, $J$ = 17.0, 1.1, 1.1 Hz, 1H), 5.35–5.23 (m, 1H), 5.26 (ddd, $J$ = 10.5, 0.9, 0.9 Hz, 1H), 5.06–4.99 (m, 1H), 4.67 (d, $J$ = 11.9 Hz, 1H), 4.58 (d, $J$ = 11.9 Hz, 1H), 4.16 (dddt, $J$ = 30.8, 13.0, 6.4, 3.3 Hz, 1H), 4.07 (dd, $J$ = 9.7, 6.1 Hz, 1H), 3.74 (dd, $J$ =

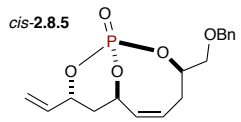
9.8, 6.4 Hz, 1H), 3.17–3.07 (m, 1H), 2.36 (ddd, $J$ = 14.0, 8.7, 2.9 Hz, 1H), 2.20 (ddd, $J$ = 14.5, 11.9, 6.0 Hz, 1H), 1.81 (ddd, $J$ = 14.5, 3.7, 1.9 Hz, 1H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 13C NMR (126 MHz, CDCl3) δ 137.9 (s), 135.0 (d, $J_{CP}$ = 10.2 Hz), 131.2 (s), 128.4 (s), 127.8 (s), 127.7 (s), 126.8 (s), 117.2 (d, $J_{CP}$ = 1.4 Hz), 78.3 (d, $J_{CP}$ = 7.2 Hz), 76.9 (d, $J_{CP}$ = 6.0 Hz), 76.0 (d, $J_{CP}$ = 5.9 Hz), 73.6 (s), 72.2 (s), 36.0 (d, $J_{CP}$ = 6.4 Hz), 29.5 (s).

**$^{31}$P NMR (162 MHz, $CDCl_3$)** δ -10.79 (dd, $J$ = 30.4, 24.7 Hz).

**HRMS:** cald. for $[C_{17}H_{21}O_5P]_2Na$ $(2M+Na)^+$ 695.2151; found 695.2125 (TOF MS ES+).

**(*1R,3R,7R,9R,Z*)-3-((benzyloxy)methyl)-9-vinyl-2,10,11-trioxa-1-phosphabicyclo[5.3.1]undec-5-ene 1-oxide (*cis*-2.8.5):**




Following General Procedure 2, triene **2.8.3** (30.0 mg, 0.0824 mmol) was exposed to G-II catalyst (3 mol %) in refluxing $CH_2Cl_2$ to provide the corresponding bicyclic phosphate *cis*-**2.8.5** (16.1 mg, 0.0479 mmol, 58% yield) as a colorless oil.

**FTIR** (neat): 2924, 2854, 1454, 1292, 1018, 743 $cm^{-1}$.

**Optical Rotation**: $[\alpha]_D$ = +3.5 ($c$ = 0.46, $CHCl_3$).

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.40–7.28 (m, 5H), 5.84 (dddd, $J$ = 17.1, 10.7, 5.3, 2.1 Hz, 1H), 5.73 (ddd, $J$ = 20.5, 8.7, 2.8 Hz, 1H), 5.50 (dd, $J$ = 11.8, 1.8 Hz, 1H), 5.41 (dd, $J$ = 17.2, 1.3 Hz, 1H), 5.34–5.23 (m, 1H), 5.26 (dd, $J$ = 10.7, 1.0 Hz, 1H), 5.03 (dd, $J$ = 11.9, 5.0 Hz, 1H), 4.73 (ddd, $J$ = 12.7, 6.8, 2.3 Hz, 1H), 4.59 (d, $J$ = 12.0 Hz, 1H), 4.54 (d, $J$ = 12.0 Hz, 1H), 3.55 (dd, $J$ = 10.0, 5.4 Hz, 1H), 3.45 (ddd, $J$ = 9.9, 7.1, 0.7 Hz, 1H),

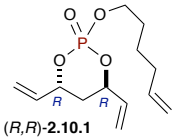
3.38–3.29 (m, 1H), 2.38 (dd, $J$ = 14.1, 8.7 Hz, 1H), 2.19 (ddd, $J$ = 14.6, 12.0, 5.9 Hz, 1H), 1.81 (dd, $J$ = 14.6, 1.9 Hz, 1H).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 137.7 (s), 135.0 (d, $J_{CP}$ = 10.0 Hz), 131.2 (s), 128.4 (s), 127.8 (s), 127.6 (s), 125.3 (s), 117.2 (d, $J_{CP}$ = 1.3 Hz), 78.3 (d, $J_{CP}$ = 7.1 Hz), 77.1 (d, $J_{CP}$ = 6.1 Hz), 73.2 (s), 72.4 (d, $J_{CP}$ = 4.8 Hz), 70.4 (d, $J_{CP}$ = 15.1 Hz), 36.2 (d, $J_{CP}$ = 6.5 Hz), 27.4 (s).

**$^{31}$P NMR (162 MHz, $CDCl_3$)** δ -9.29.

**HRMS:** cald. for $[C_{17}H_{21}O_5P]_2Na$ $(2M+Na)^+$ 695.2151; found 695.2162 (TOF MS ES+).

**(4*R*,6*R*)-2-(hex-5-en-1-yloxy)-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide (2.10.1):**



(*R,R*)-**2.10.1**

Following General Procedure 1, monochlorophosphate (*R,R*)-**2.2A** (0.624 g, 2.99 mmol) and 5-hexen-1-ol (0.272 g, 2.719 mmol) were converted into triene **2.10.1** (0.517 g, 1.90 mmol, 70% yield) which was isolated as a colorless oil.

**FTIR** (neat): 3078, 2935, 1429, 1283, 1119, 1011, 926, 874, 845 $cm^{-1}$;

**Optical Rotation**: $[\alpha]_D$ = –50.4° ($c$ = 1.66 , $CHCl_3$).

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.02 (dddd, $J$ = 17.3, 10.6, 6.0, 0.6 Hz, 1H, $H_2C$=C<u>H</u>-CHO(P)$CH_2$), 5.92 (dddd, $J$ = 17.4, 10.6, 5.2, 1.6 Hz, 1H, $H_2C$=C<u>H</u>-CHO(P)$CH_2$), 5.79 (ddt, $J$ = 17.0, 10.2, 6.7 Hz, 1H, $H_2C$=C<u>H</u>-$CH_2$-$CH_2$-$CH_2$-$CH_2$-O(P)), 5.46 (ddd, $J$ = 17.1, 1.5, 1.0 Hz, 1H, <u>$H_a$</u>$H_b$C=CH-CHO(P)$CH_2$), 5.38 (ddd, $J$ = 17.2, 1.4, 1.0Hz, 1H, $H_a$<u>$H_b$</u>C=CH-CHO(P)$CH_2$), 5.31 (ddd, $J$ = 4.6, 1.3, 1.3 Hz, 1H, <u>$H_a$</u>$H_b$C=CH-CHO(P)$CH_2$), 5.29 (ddd, $J$ = 4.5, 1.2, 1.2 Hz, 1H, $H_a$<u>$H_b$</u>C=CH-CHO(P)$CH_2$), 5.08 – 4.94 (m, 4H,

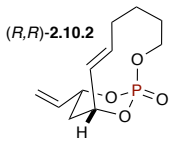
$\underline{H_2}C$=CH-$CH_2$-$CH_2$-$CH_2$-$CH_2$-O(P), $H_2C$=CH-C$\underline{H}$O(P)$CH_2$, $H_2C$=CH-C$\underline{H}$O(P)$CH_2$), 4.11 (dtd, *J* = 7.7, 6.5, 2.5 Hz, 2H, $H_2C$=CH-$CH_2$-$CH_2$-$CH_2$-$\underline{C}H_2$-O(P)), 2.17 (dddd, *J* = 14.7, 8.1, 4.9, 1.5 Hz, 1H, $H_2C$=CH-CHO(P)C$\underline{H}_aH_b$CHO[P]), 2.12 – 2.02 (m, 3H, $H_2C$=CH-CHO(P)$CH_a\underline{H}_b$CHO[P], $H_2C$=CH-C$\underline{H_2}$-$CH_2$-$CH_2$-$CH_2$-O(P)), 1.75 – 1.67 (m, 2H, $H_2C$=CH-$CH_2$-$CH_2$-C$\underline{H_2}$-$CH_2$-O(P)), 1.53 – 1.45 (m, 2H, $H_2C$=CH-$CH_2$-C$\underline{H_2}$-$CH_2$-$CH_2$-O(P)).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 138.2, 135.0 (d, $J_{CP}$ = 4.2 Hz), 135.0, 118.0, 117.4, 114.9, 77.5 (d, *J* = 6.7 Hz), 76.1 (d, $J_{CP}$ = 6.1 Hz), 67.8 (d, $J_{CP}$ = 5.9 Hz), 35.2 (d, $J_{CP}$ = 7.6 Hz), 33.1, 29.6 (d, $J_{CP}$ = 6.6 Hz), 24.7.

**$^{31}$P NMR (162 MHz, $CDCl_3$)** δ –7.55;

**HRMS:** cald. for $C_{13}H_{21}O_4P$ $(M+Na)^+$ 295.1075; found 295.1082 (TOF MS ES+).

**(1*R*,9*R*,11*R*,*E*)-11-vinyl-2,12,13-trioxa-1-phosphabicyclo[7.3.1]tridec-7-ene 1-oxide (2.10.2):**




Following General Procedure 2, triene **2.10.1** (50.0 mg, 0.184 mmol) was exposed to G-II catalyst (2 mol %, portion-wise over 5 hours) in refluxing $CH_2Cl_2$ to provide the corresponding bicyclic phosphate **2.10.2** (18.8 mg, 0.0770 mmol, 42% yield, 74% based upon recovered starting material, colorless oil), along with unreacted **2.10.1** (21.7 mg, 0.080mmol).

**Yield:** 42% (74% brsm).

**FTIR** (neat): 2928, 2856, 1286, 1057, 1022, 995, 960, 927, 899 $cm^{-1}$;

**Optical Rotation**: $[\alpha]_D = -33.0°$ ($c = 0.46$, $CHCl_3$).

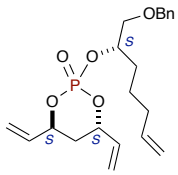
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.28 (dddd, $J$ = 16.4, 9.7, 5.2, 1.7 Hz, 1H, $H_2C$-HC=C<u>H</u>-CHO(P)$CH_2$), 5.92 – 5.83 (m, 2H, $H_2C$-HC=C<u>H</u>-CHO(P)$CH_2$, $H_2C$=C<u>H</u>-CHO[P]), 5.44 (ddd, $J$ = 17.2, 1.3, 1.3 Hz, 1H, <u>$H_a$</u>$H_b$C=CH-CHO[P]), 5.27 (ddd, $J$ = 10.6, 1.2, 1.2 Hz, 1H, $H_a$<u>$H_b$</u>C=CH-CHO[P]), 5.22 – 5.09 (m, 2H, HC=CH-C<u>H</u>O(P)$CH_2$, HC=CH-C<u>H</u>O(P)$CH_2$), 4.22 (ddd, $J$ = 10.4, 6.7, 2.6 Hz, 1H, HC=CH-$CH_2$-$CH_2$-$CH_2$-C<u>$H_a$</u>$H_b$-O(P)), 3.82 – 3.77 (m, 1H, HC=CH-$CH_2$-$CH_2$-$CH_2$-$CH_a$<u>$H_b$</u>-O(P)), 2.40 – 2.31 (m, 1H, HC=CH-C<u>$H_a$</u>$H_b$-$CH_2$-$CH_2$-$CH_2$-O(P)), 2.24 (ddd, $J$ = 14.6, 12.0, 5.2 Hz, 1H, HC=CH-CHO(P)C<u>$H_a$</u>$H_b$CHO[P]), 2.20 – 2.11 (m, 1H, HC=CH-$CH_a$<u>$H_b$</u>-$CH_2$-$CH_2$-$CH_2$-O(P)), 2.00 – 1.88 (m, 2H, HC=CH-$CH_2$-C<u>$H_a$</u>$H_b$-$CH_2$-$CH_2$-O(P), HC=CH-$CH_2$-$CH_2$-C<u>$H_a$</u>$H_b$-$CH_2$-O(P)), 1.85 (ddd, $J$ = 14.5, 3.6, 2.0 Hz, 1H, HC=CH-CHO(P)$CH_a$<u>$H_b$</u>CHO[P]), 1.64 – 1.56 (m, 2H, HC=CH-$CH_2$-$CH_a$<u>$H_b$</u>-$CH_2$-$CH_2$-O(P), HC=CH-$CH_2$-$CH_2$-$CH_a$<u>$H_b$</u>-$CH_2$-O(P)).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 138.9, 135.3 (d, $J_{CP}$ = 10.1 Hz), 127.8, 117.1 (d, $J_{CP}$ = 1.3 Hz), 76.4 (d, $J_{CP}$ = 6.4 Hz), 75.3 (d, $J_{CP}$ = 7.2 Hz), 66.2 (d, $J_{CP}$ = 5.5 Hz), 35.2 (d, $J_{CP}$ = 6.0 Hz), 32.4, 29.0 (d, $J_{CP}$ = 10.1 Hz), 28.6.

**$^{31}$P NMR (162 MHz, $CDCl_3$)** δ –8.44;

**HRMS:** cald. for $C_{11}H_{17}O_4P$ $(M+Na)^+$ 267.0762; found 267.0759 (TOF MS ES+).

**(4*S*,6*S*)-2-(((*S*)-1-(benzyloxy)hept-6-en-2-yl)oxy)-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide ((*S,S,S*)-2.10.3):**




(*S,S,S*)-**2.10.3**

Following General Procedure 1, monochlorophosphate (*S,S*)-**2.2A** (0.104 g, 0.497 mmol) and alcohol (*S*)-**2.10.5**[5] (0.131 g, 0.596 mmol) were converted into triene **2.10.3** (0.071 g, 0.181 mmol, 36% yield) which was isolated as a colorless oil.

**FTIR** (neat): 3074, 3030, 2932, 2862, 1454, 1285, 1119, 1070, 1004, 926, 737, 700 $cm^{-1}$;

**Optical Rotation**: $[\alpha]_D$ = +49.9° (*c* = 1.35, $CHCl_3$).

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.30 – 7.21 (m, 5H, aromatic C–H), 6.01 (dddd, *J* = 17.0, 10.6, 6.3, 0.8 Hz, 1H, $H_2C$=C<u>H</u>-CHO(P)$CH_2$), 5.81 – 5.68 (m, 2H, $H_2C$=C<u>H</u>-CHO(P)$CH_2$, $H_2C$=C<u>H</u>-$CH_2$-$CH_2$-$CH_2$-CHO(P)$CH_2$OBn), 5.31 (ddd, *J* = 4.2, 1.3, 1.3 Hz, 1H, <u>H</u>$_a$H$_b$C=CH-CHO(P)$CH_2$), 5.28 (ddd, *J* = 4.2, 1.2, 1.2 Hz, 1H, H$_a$<u>H</u>$_b$C=CH-CHO(P)$CH_2$), 5.22 (dt, *J* = 10.6, 1.2 Hz, 1H, <u>H</u>$_a$H$_b$C=CH-CHO(P)$CH_2$), 5.17 (ddd, *J* = 10.6, 1.2, 1.2 Hz, 1H, H$_a$<u>H</u>$_b$C=CH-CHO(P)$CH_2$), 5.00 – 4.92 (m, 3H, <u>H</u>$_2$C=CH-$CH_2$-$CH_2$-$CH_2$, $H_2C$=CH-C<u>H</u>O(P)$CH_2$), 4.90 (ddt, *J* = 10.2, 2.3, 1.2 Hz, 1H, $H_2C$=CH-C<u>H</u>O(P)$CH_2$), 4.59 – 4.43 (m, 1H, C<u>H</u>O(P)$CH_2$OBn), 4.52 (d, *J* = 12.0 Hz, 1H, OC<u>H</u>$_a$H$_b$Ph), 4.45 (d, *J* = 12.0 Hz, 1H, OCH$_a$<u>H</u>$_b$Ph), 3.57 – 3.49 (m, 2H, CHO(P)C<u>H</u>$_2$OBn), 2.08 – 2.00 (m, 3H, $H_2C$=CH-C<u>H</u>$_2$-$CH_2$-$CH_2$, $H_2C$=CH-CHO(P)C<u>H</u>$_a$H$_b$CHO[P]), 1.96 (dddd, *J* = 14.7, 5.5, 3.9, 1.8 Hz, 1H $H_2C$=CH-

[5] Ida, A.; Hoshiya, N.; Uenishi, J. Investigation of Pd(II)-Catalyzed Cyclization of Chiral θ-Hydroxy-α,β,γ,δ-unsaturated Dienol. *Heterocycles* **2015**, *90*, 1082–1093.

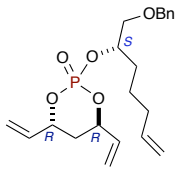
CHO(P)$CH_a\underline{H}_bCHO$[P]), 1.76 – 1.60 (m, 2H, $H_2C$=CH-$CH_2$-$CH_2$-$C\underline{H}_2$-CHO(P)$CH_2$OBn), 1.52 – 1.37 (m, 2H, $H_2C$=CH-$CH_2$-$C\underline{H}_2$-$CH_2$-CHO(P)$CH_2$OBn).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 138.24, 137.88, 135.2 (d, $J_{CP}$ = 7.8 Hz), 135.2 (d, $J_{CP}$ = 3.2 Hz), 128.3 (2C), 127.68 (2C), 127.65, 117.8, 117.0, 114.8, 78.0 (d, $J_{CP}$ = 6.1 Hz), 77.9 (d, $J_{CP}$ = 6.6 Hz), 75.7 (d, $J_{CP}$ = 6.1 Hz), 73.2, 71.8 (d, $J_{CP}$ = 4.4 Hz), 35.3 (d, $J_{CP}$ = 7.4 Hz), 33.4, 31.7 (d, $J_{CP}$ = 4.8 Hz), 24.18.

**$^{31}$P NMR (162 MHz, $CDCl_3$)** δ – 7.89;

**HRMS:** cald. for $C_{21}H_{29}O_5P$ $(M+Na)^+$ 415.1650; found 415.1649 (TOF MS ES+).

**(4*R*,6*R*)-2-(((*S*)-1-(benzyloxy)hept-6-en-2-yl)oxy)-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide ((*S,S,R*)-2.10.4):**



(*S,S,R*)-**2.10.4**

Following General Procedure 1, monochlorophosphate (*S,S*)-**2.2A** (0.104 g, 0.497 mmol) and alcohol (*S*)-**2.10.5** (0.131 g, 0.596 mmol) were converted into triene **2.10.4** (0.0923 g, 0.235 mmol, 47% yield) which was isolated as a pale yellow oil.

**FTIR** (neat): 3076, 3030, 2930, 2862, 1722, 1641, 1454,1429, 1283, 1119, 1070, 1003, 927, 872, 735, 698 $cm^{-1}$;

**Optical Rotation**: $[\alpha]_D$ = –37.2° (*c* = 0.58 , $CHCl_3$).

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.38 – 7.25 (m, 5H, aromatic C–H), 6.02 (dddd, *J* = 17.2, 10.6, 6.0, 0.6 Hz, 1H, $H_2C$=C$\underline{H}$-CHO(P)$CH_2$), 5.92 (dddd, *J* = 17.3, 10.6, 5.3, 1.6 Hz, 1H, $H_2C$=C$\underline{H}$-CHO(P)$CH_2$), 5.78 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H, $H_2C$=C$\underline{H}$-$CH_2$-$CH_2$-

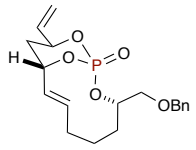
$CH_2$-CHO(P)$CH_2$OBn), 5.46 (ddd, *J* = 17.1, 1.2, 1.2 Hz, 1H, $\underline{H}_aH_bC$=CH-CHO(P)$CH_2$), 5.36 (ddd, *J* = 17.2, 1.2, 1.2 Hz, 1H, $H_a\underline{H}_bC$=CH-CHO(P)$CH_2$), 5.30 (ddd, *J* = 10.6, 1.2, 1.2 Hz, 1H, $H_a\underline{H}_bC$=CH-CHO(P)$CH_2$), 5.23 (ddd, *J* = 10.6, 1.2, 1.2 Hz, 1H, $\underline{H}_aH_bC$=CH-CHO(P)$CH_2$), 5.08 – 4.94 (m, 4H, $\underline{H}_2C$=CH-$CH_2$-$CH_2$-$CH_2$, $H_2C$=CH-C$\underline{H}$O(P)$CH_2$, $H_2C$=CH-C$\underline{H}$O(P)$CH_2$), 4.67 – 4.61 (m, 1H, C$\underline{H}$O(P)$CH_2$OBn), 4.60 (d, *J* = 12.0 Hz, 1H, OC$\underline{H}_aH_b$Ph), 4.54 (d, *J* = 12.0 Hz, 1H, OC$H_a\underline{H}_b$Ph), 3.62 (dd, *J* = 4.8, 1.9 Hz, 2H, CHO(P)C$\underline{H}_2$OBn), 2.19 – 2.04 (m, 4H, $H_2C$=CH-C$\underline{H}_2$-$CH_2$-$CH_2$, $H_2C$=CH-CHO(P)C$\underline{H}_2$CHO[P]), 1.77 – 1.71 (m, 2H, $H_2C$=CH-$CH_2$-$CH_2$-C$\underline{H}_2$-CHO(P)$CH_2$OBn), 1.58 – 1.42 (m, 2H, $H_2C$=CH-$CH_2$-C$\underline{H}_2$-$CH_2$-CHO(P)$CH_2$OBn).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 138.2, 138.1, 135.3 (d, $J_{CP}$ = 3.7 Hz), 135.1 (d, $J_{CP}$ = 7.2 Hz), 128.3 (2C), 127.61 (2C), 127.59, 117.7, 117.4, 114.9, 78.4 (d, $J_{CP}$ = 6.4 Hz), 77.5 (d, $J_{CP}$ = 6.5 Hz), 76.1 (d, $J_{CP}$ = 6.2 Hz), 73.2, 71.7 (d, $J_{CP}$ = 4.0 Hz), 35.3 (d, $J_{CP}$ = 7.5 Hz), 33.4, 31.6 (d, $J_{CP}$ = 5.0 Hz), 24.2.

**$^{31}$P NMR (162 MHz, $CDCl_3$)** δ – 8.00;

**HRMS:** cald. for $C_{21}H_{29}O_5P$ $(M+Na)^+$ 415.1650; found 415.1634 (TOF MS ES+).

**(1*S*,3*S*,9*S*,11*S*,*E*)-3-((benzyloxy)methyl)-11-vinyl-2,12,13-trioxa-1-phosphabicyclo[7.3.1]tridec-7-ene 1-oxide (*cis*-2.10.6):**




Following General Procedure 2, triene **2.10.3** (25.0 mg, 0.0637 mmol) was exposed to G-II catalyst (3 mol %, portion-wise over 5 hours) in refluxing $CH_2Cl_2$ to provide the corresponding bicyclic phosphate **2.10.6** (16.7 mg, 0.0458 mmol, 72% yield) as a white,

crystalline solid. The solid was re-crystallized via vapor diffusion method (EtOAc:Hexanes, -5°C, overnight) to obtain X-ray quality crystals.[6] Note: Several recrystallization procedures were attempted to try to improve the crystal size, as most attempts resulted in crystals that were very thin. Vapor-diffusion was decidedly the best procedure, and as such, was used for the recrystallization of other large-ring containing bicyclic phosphates described herein (*vide infra*).

**m.p.** 114 – 116 °C

**FTIR** (neat): 3029, 2928, 2856, 1285, 1122, 1097, 984, 960, 897, 852, 698 $cm^{-1}$;

**Optical Rotation**: $[\alpha]_D = +57.3°$ ($c = 0.11$, $CHCl_3$).

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 5H, aromatic C-H), 6.23 (dddd, $J$ = 15.5, 10.9, 4.6, 1.7 Hz, 1H, $H_2C$-HC=C<u>H</u>-CHO(P)$CH_2$), 5.92 – 5.82 (m, 2H, $H_2C$-<u>H</u>C=CH-CHO(P)$CH_2$, $H_2C$=C<u>H</u>-CHO[P]), 5.44 (ddd, $J$ = 17.1, 1.3, 1.3 Hz, 1H, <u>$H_a$</u>$H_b$C=CH-CHO[P]), 5.27 (ddd, $J$ = 10.6, 1.1, 1.1 Hz, 1H, $H_a$<u>$H_b$</u>C=CH-CHO[P]), 5.19 – 5.10 (m, 2H, HC=CH-C<u>H</u>O(P)$CH_2$, HC=CH-C<u>H</u>O(P)$CH_2$), 4.59 (d, $J$ = 11.9 Hz, 1H, OC<u>$H_a$</u>$H_b$Ph), 4.55 (d, $J$ = 12.2 Hz, 1H, OC$H_a$<u>$H_b$</u>Ph), 4.14 – 4.08 (m, 1H, C<u>H</u>O(P)$CH_2$OBn), 3.85 (dd, $J$ = 9.7, 3.4 Hz, 1H, CHO(P)C<u>$H_a$</u>$H_b$OBn), 3.67 (dd, $J$ = 9.7, 6.9 Hz, 1H, CHO(P)C$H_a$<u>$H_b$</u>OBn), 2.49 – 2.43 (m, 1H, $H_2C$=CH-C<u>$H_a$</u>$H_b$-$CH_2$-$CH_2$), 2.29 – 2.17 (m, 2H, $H_2C$=CH-CHO(P)C<u>$H_a$</u>$H_b$CHO[P], $H_2C$=CH-$CH_2$-$CH_2$-C<u>$H_a$</u>$H_b$-CHO(P)$CH_2$OBn), 2.08 – 1.98 (m, 1H, $H_2C$=CH-C$H_a$<u>$H_b$</u>-$CH_2$-$CH_2$), 1.92 – 1.86 (m, 1H, $H_2C$=CH-$CH_2$-C$H_a$<u>$H_b$</u>-$CH_2$), 1.83 (ddd, $J$ = 14.6, 3.7, 2.3 Hz, 1H, $H_2C$=CH-CHO(P)C<u>$H_a$</u>$H_b$CHO[P]),

[6] All X-ray crystallographic data has been submitted to the Cambridge Crystallographic Data Centre, and the structure for *cis*-**2.10.6** was assigned the following deposition number: 1058400.

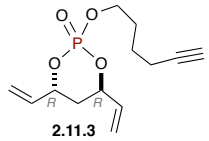
1.54 – 1.44 (m, 2H, $H_2C$=CH-$CH_2$-$CH_2$-$CH_a\underline{H}_b$-CHO(P)$CH_2$OBn, $H_2C$=CH-$CH_2$-$CH_a\underline{H}_b$-$CH_2$-).

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 139.3, 138.2, 135.3 (d, $J_{CP}$ = 10.1 Hz), 128.3 (2C), 128.2, 127.7 (2C), 127.6, 117.1, 78.0 (d, $J_{CP}$ = 5.9 Hz), 76.3 (d, $J_{CP}$ = 6.3 Hz), 75.5 (d, $J_{CP}$ = 7.2 Hz), 73.5, 72.3, 35.3 (d, $J_{CP}$ = 5.9 Hz), 33.8, 32.8 (d, $J_{CP}$ = 9.1 Hz), 27.8.

**$^{31}$P NMR (162 MHz, $CDCl_3$)** δ – 9.80.

**HRMS:** cald. for $C_{19}H_{25}O_5P$ $(M+Na)^+$ 387.1337; found 387.1325 (TOF MS ES+).

**(4*R*,6*R*)-2-(hex-5-yn-1-yloxy)-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide (2.11.3)**




2.11.3

Following General Procedure 1, monochlorophosphate (*R,R*)-**2.2A** (0.4210 g, 2.018 mmol) and 5-hexyn-1-ol (0.1816 g, 1.850 mmol) were converted to phosphate triene **2.11.3** (0.3562 g, 1.318 mmol, 65%) which was isolated as a colorless oil.

**FTIR (neat)**: 3296, 3234, 2955, 2939, 2870, 1431, 1281, 1119, 1020, 993, 932, 874, 847, 725, 644, 548 $cm^{-1}$;

**Optical Rotation:** $[\alpha]_D$ = –49.1 (*c* 1.96, $CHCl_3$);

**$^1$H NMR (500 MHz, $CDCl_3$)** δ ppm 6.00 (ddd, *J* = 16.9, 10.6, 6.0 Hz, 1H, $H_2C$=C$\underline{H}$-CHO(P)$CH_2$), 5.89 (dddd, *J* = 17.3, 10.6, 5.2, 1.6 Hz, 1H, $H_2C$=C$\underline{H}$-CHO(P)$CH_2$), 5.44 (ddd, *J* = 17.0, 1.2, 1.2 Hz, 1H, $\underline{H}$-HC=CH-CHO(P)$CH_2$), 5.36 (ddd, *J* = 17.2, 1.2, 1.2 Hz, 1H, $\underline{H}$-HC=CH-CHO(P)$CH_2$), 5.31–5.26 (m, 2H, $\underline{H}$-HC=CH-CHO(P)$CH_2$, $\underline{H}$-HC=CH-CHO(P)$CH_2$), 5.06–4.93 (m, 2H, $H_2C$=CH-C$\underline{H}$O(P)$CH_2$, $H_2C$=CH-C$\underline{H}$O(P)$CH_2$), 4.13–4.06 (m, 2H, (P)OC$\underline{H}_2CH_2CH_2CH_2CCH$), 2.21 (td, *J* = 7.0, 2.7 Hz,

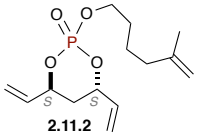
2H, (P)$OCH_2CH_2CH_2C\underline{H_2}CCH$), 2.15 (dddd, $J$ = 14.7, 8.2, 4.9, 1.6 Hz, 1H, $H_2C$=CH-CHO(P)$C\underline{H_a}H_bCHO$[P]), 2.03 (dddd, $J$ = 14.8, 5.5, 3.6, 1.9 Hz, 1H, $H_2C$=CH-CHO(P)$CH_a\underline{H_b}CHO$[P]), 1.94 (t, $J$ = 2.6 Hz, 1H, (P)$OCH_2CH_2CH_2CH_2CC\underline{H}$), 1.79 (dt, $J$ = 12.5, 6.4 Hz, 2H, (P)$OCH_2CH_2C\underline{H_2}C\underline{H_2}CCH$), 1.61 (p, $J$ = 7.2 Hz, 2H, (P)$OCH_2CH_2C\underline{H_2}C\underline{H_2}CCH$);

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ ppm 134.86 (d, $J_{CP}$ = 10.9 Hz, CH), 134.85 (CH), 118.1 ($CH_2$), 117.4 ($CH_2$), 83.6 (C), 77.5 (d, $J_{CP}$ = 6.7 Hz, CH), 76.1 (d, $J_{CP}$ = 6.2 Hz, CH), 68.7 (CH), 67.2 (d, $J_{CP}$ = 5.9 Hz, $CH_2$), 35.0 (d, $J_{CP}$ = 7.7 Hz, $CH_2$), 29.1 (d, $J_{CP}$ = 6.9 Hz, $CH_2$), 24.4 ($CH_2$), 17.8 ($CH_2$);

**$^{31}$P NMR (162 MHz, $CDCl_3$)** δ ppm –7.66 (dq, $J_{PH}$ = 13.9, 6.9 Hz);

**HRMS (TOF MS ES+)** calcd for $(C_{13}H_{19}O_4P)_2Na$ $(2M+Na)^+$ 563.1940; found 563.1929.

**(4*S*,6*S*)-2-((5-methylhex-5-en-1-yl)oxy)-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide (2.11.2):**



**2.11.2**

Following General Procedure 1, monochlorophosphate (*S,S*)-**2.2A** (0.3380 g, 1.620 mmol) and 5-methyl-5-penten-1-ol (0.1700 g, 1.485 mmol) were converted to phosphate triene **2.11.2** (0.2634 g, 0.9200 mmol, 68%) which was isolated as a colorless oil.

**FTIR (neat)**: 2937, 2868, 1429, 1412, 1283, 1119, 1018, 926, 876, 849, 725, 646, 546 $cm^{-1}$;

**Optical Rotation:** $[\alpha]_D$ = +51.7 (*c* 1.27, $CHCl_3$);

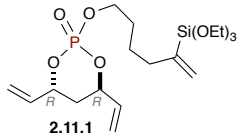
**$^{1}$H NMR (500 MHz, $CDCl_3$)** δ ppm 6.03 (ddd, $J$ = 16.9, 10.6, 6.0 Hz, 1H, $H_2C$=C<u>H</u>-CHO(P)$CH_2$), 5.91 (ddddd, $J$ = 17.3, 10.7, 5.3, 1.5, 1.5 Hz, 1H, $H_2C$=C<u>H</u>-CHO(P)$CH_2$), 5.46 (dd, $J$ = 17.2, 1.3 Hz, 1H, <u>H</u>-HC=CH-CHO(P)$CH_2$), 5.37 (dd, $J$ = 17.2, 1.3 Hz, 1H, <u>H</u>-HC=CH-CHO(P)$CH_2$), 5.31 (dd, $J$ = 4.3, 1.2 Hz, 1H, <u>H</u>-HC=CH-CHO(P)$CH_2$), 5.29 (dd, $J$ = 4.3, 1.2 Hz, 1H, <u>H</u>-HC=CH-CHO(P)$CH_2$), 5.07–5.01 (m, 1H, $H_2C$=CH-C<u>H</u>O(P)$CH_2$), 5.00–4.94 (m, 1H, $H_2C$=CH-C<u>H</u>O(P)$CH_2$), 4.71 (d, $J$ = 2.1 Hz, 1H, (P)O$CH_2CH_2CH_2CH_2C(CH_3)$=C<u>H</u>$_a$H$_b$), 4.67–4.66 (m, 1H, (P)O$CH_2CH_2CH_2CH_2C(CH_3)$=C<u>H</u>$_a$H$_b$), 4.13–4.08 (m, 2H, (P)OC<u>H</u>$_2$$CH_2CH_2CH_2C(CH_3)$=$CH_2$), 2.21–2.13 (m, 1H, $H_2C$=CH-CHO(P)C<u>H</u>$_a$H$_b$CHO[P]),), 2.07–2.01 (m, 3H, $H_2C$=CH-CHO(P)$CH_a$<u>H</u>$_b$CHO[P], (P)O$CH_2CH_2CH_2$C<u>H</u>$_2$$C(CH_3)$=$CH_2$), 1.71–1.66 (m, 5H, (P)O$CH_2CH_2CH_2CH_2C$(C<u>H</u>$_3$)=$CH_2$, (P)O$CH_2$C<u>H</u>$_2$$CH_2CH_2C(CH_3)$=$CH_2$), 1.53 (dtd, $J$ = 8.8, 7.3, 5.5 Hz, 2H, (P)O$CH_2CH_2$C<u>H</u>$_2$$CH_2C(CH_3)$=$CH_2$);

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ ppm 145.2 (C), 135.0 (d, $J_{CP}$ = 4.7 Hz, CH), 134.96 (CH), 118.0 ($CH_2$), 117.4 ($CH_2$), 110.2 ($CH_2$), 77.5 (d, $J_{CP}$ = 6.8 Hz, CH), 76.1 (d, $J_{CP}$ = 6.0 Hz, CH), 67.8 (d, $J_{CP}$ = 6.0 Hz, $CH_2$), 37.1 ($CH_2$), 35.1 (d, $J_{CP}$ = 7.6 Hz, $CH_2$), 29.8 (d, $J_{CP}$ = 6.8 Hz, $CH_2$), 23.3 ($CH_2$), 22.2 ($CH_3$);

**$^{31}$P NMR (162 MHz, $CDCl_3$)** δ ppm –7.55 (dd, $J_{PH}$ = 14.2, 7.1 Hz);

**HRMS (TOF MS ES+)** calcd for $(C_{14}H_{23}O_4P)_2Na$ $(2M+Na)^+$ 595.2566; found 595.2557.

**(4*R*,6*R*)-2-((5-(triethoxysilyl)hex-5-en-1-yl)oxy)-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide (2.11.1):**




**2.11.1**

To a clean, dry round bottom flask, equipped with a magnetic stirbar, was added **2.11.3** (0.0720 g, 0.2664 mmol) and $CH_2Cl_2$ (dry, degassed, 3 mL) under Ar. The flask was cooled to 0 °C, where $(Cp^*Ru[MeCN]_3)PF_6$ (6.7 mg, 0.01332 mmol, 5 mol %) was added in two portions. The flask was removed from the cooling bath and warmed to room temperature. The reaction stirred at room temperature for 1 hour (monitored by TLC) and, upon completion, concentrated under reduced pressure. The crude mixture was separated via flash chromatography (silica, 0% to 50% EtOAc in Hexanes) to afford **2.11.1** (0.0791 g, 0.1820 mmol, 68%) as a colorless oil. **2.11.1** was stored in dry, degassed toluene under Ar in a flammable freezer for further use, as storage neat under Ar at lower temperatures resulted in decomposition after 2 weeks.

**FTIR (neat):** 2974, 2925, 2895, 1285, 1101, 1078, 1020, 991, 960, 781, 752, 550 $cm^{-1}$;

**Optical Rotation:** $[\alpha]_D = -28.6$ (*c* 0.37, benzene);

**$^1$H NMR (500 MHz, $CDCl_3$)** δ ppm 6.01 (ddd, $J_{PH}$ = 16.7, 10.4, 5.9 Hz, 1H, $H_2C$=C<u>H</u>-CHO(P)$CH_2$), 5.89 (dddd, *J* = 17.2, 10.6, 5.2, 2.0 Hz, 1H, $H_2C$=C<u>H</u>-CHO(P)$CH_2$), 5.70 (dd, *J* = 3.6, 1.8 Hz, 1H, –C[Si(OEt)$_3$]=C<u>H$_a$</u>H$_b$), 5.62 (d, *J* = 3.2 Hz, 1H–C[Si(OEt)$_3$]=C<u>H$_a$</u>H$_b$), 5.45 (dd, *J* = 16.9, 1.9 Hz, 1H, <u>H</u>-HC=CH-CHO(P)$CH_2$), 5.36 (dd, *J* = 17.2, 0.7 Hz, 1H, <u>H</u>-HC=CH-CHO(P)$CH_2$), 5.31–5.26 (m, 2H, <u>H</u>-HC=CH-CHO(P)$CH_2$, <u>H</u>-HC=CH-CHO(P)$CH_2$), 5.05–4.99 (m, 1H, $H_2C$=CH-C<u>H</u>O(P)$CH_2$), 4.98–4.93 (m, 1H, $H_2C$=CH-C<u>H</u>O(P)$CH_2$), 4.14–4.04 (m, 2H,

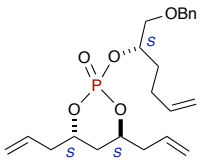
(P)OC$\underline{H}_2$CH$_2$CH$_2$CH$_2$C[Si(OEt)$_3$]=CH$_2$), 3.80 (dtt, $J$ = 9.3, 4.5, 2.2 Hz, 6H, –Si(OC$\underline{H}_2$CH$_3$)$_3$), 2.21–2.11 (m, 3H, H$_2$C=CH-CHO(P)C$\underline{H}_a$H$_b$CHO[P]), (P)OCH$_2$CH$_2$CH$_2$C$\underline{H}_2$C[Si(OEt)$_3$]=CH$_2$), 2.06–2.00 (m, 1H, H$_2$C=CH-CHO(P)C$\underline{H}_a$H$_b$CHO[P]), 1.68 (q, $J$ = 7.0, 6.4 Hz, 2H, (P)OCH$_2$C$\underline{H}_2$C$\underline{H}_2$CH$_2$C[Si(OEt)$_3$]=CH$_2$), 1.54 (tt, $J$ = 9.6, 6.3 Hz, 2H, (P)OCH$_2$C$\underline{H}_2$C$\underline{H}_2$CH$_2$C[Si(OEt)$_3$]=CH$_2$), 1.21 (td, $J$ = 7.0, 2.0 Hz, 9H, –Si(OCH$_2$C$\underline{H}_3$)$_3$).;

**$^{13}$C NMR (126 MHz, CDCl$_3$)** δ ppm 143.0 (C), 134.98 (d, $J_{CP}$ = 9.6 Hz, CH), 134.96 (CH), 129.4 (CH$_2$), 118.0 (CH$_2$), 117.4 (CH$_2$), 77.5 (d, $J_{CP}$ = 6.8 Hz, CH), 76.0 (d, $J_{CP}$ = 6.0 Hz, CH), 67.8 (d, $J_{CP}$ = 6.0 Hz, CH$_2$), 58.4 (3 x CH$_2$), 35.3 (CH$_2$), 35.1 (d, $J_{CP}$ = 7.7 Hz, CH$_2$), 29.9 (d, $J_{CP}$ = 6.8 Hz, CH$_2$), 24.5 (CH$_2$), 18.1 (3 x CH$_3$);

**$^{31}$P NMR (162 MHz, CDCl$_3$)** δ ppm –7.58 (dd, $J_{PH}$ = 13.9, 7.0 Hz);

**HRMS (TOF MS ES+)** calcd for $(C_{19}H_{35}O_7PSi)_2Na$ $(2M+Na)^+$ 891.3677; found 891.3659.

**(4*S*,6*S*)-4,6-diallyl-2-(((S)-1-(benzyloxy)hex-5-en-2-yl)oxy)-1,3,2-dioxaphosphinane 2-oxide (2.12.1):**




(*S,S,S*)-**2.12.1**

Following General Procedure 1, monochlorophosphate (*S,S*)-**2.12.3**[7] (0.182 g, 0.769 mmol) and alcohol (*S*)-**2.12.4**[8] (0.145 g, 0.705 mmol) were converted into **2.12.1** (0.211 g, 0.519 mmol, 81%) which was isolated as a pale yellow oil.

**FTIR (neat):** 2976, 2930, 2860, 1452, 1362, 1286, 1097, 997, 918, 739, 698, 629, 505 $cm^{-1}$;

**Optical Rotation:** $[\alpha]_D = -34.4$ (*c* 1.85, $CHCl_3$);

**$^1$H NMR (500 MHz, $CDCl_3$)** δ ppm 7.37–7.26 (m, 5H, Aromatic C-H), 5.86–5.69 (m, 3H, $H_2C$=C<u>H</u>-$CH_2$-$CH_2$-CHO(P)$CH_2$OBn, $H_2C$=C<u>H</u>-$CH_2$-CHO(P)$CH_2$, $H_2C$=C<u>H</u>-$CH_2$-CHO(P)$CH_2$), 5.16 (dd, *J* = 8.7, 2.1 Hz, 1H, <u>H</u>$_a$H$_b$C=CH-$CH_2$CHO(P)$CH_2$), 5.14–5.11 (m, 2H, H$_a$<u>H</u>$_b$C=CH-$CH_2$CHO(P)$CH_2$, <u>H</u>$_a$H$_b$C=CH-$CH_2$CHO(P)$CH_2$), 5.10 (dd, *J* = 3.2, 1.6 Hz, 1H, H$_a$<u>H</u>$_b$C=CH-$CH_2$CHO(P)$CH_2$), 5.05 (dq, *J* = 17.2, 1.5 Hz, 1H, <u>H</u>$_a$H$_b$C=CH-$CH_2$-$CH_2$-CHO(P)$CH_2$OBn), 4.99 (dt, *J* = 10.2, 1.5 Hz, 1H, H$_a$<u>H</u>$_b$C=CH-$CH_2$-$CH_2$-CHO(P)$CH_2$OBn), 4.66–4.48 (m, 5H, $H_2C$=CH$CH_2$-C<u>H</u>O(P)$CH_2$, $H_2C$=CH$CH_2$-C<u>H</u>O(P)$CH_2$, C<u>H</u>O(P)$CH_2$OBn, O<u>C</u>H$_2$Ph), 3.63–3.60 (m, 2H, CHO(P)<u>C</u>H$_2$OBn), 2.66–2.52 (m, 2H, $H_2C$=CH-<u>C</u>H$_2$CHO(P)$CH_2$, $H_2C$=CH-<u>C</u>H$_2$CHO(P)$CH_2$), 2.39 (dt, *J* = 14.6,

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[7] Chegondi, R.; Maitra, S.; Markley, J. L.; Hanson, P. R. Phosphate-Tether-Mediated Ring-Closing Metathesis for the Preparation of Complex 1,3-*anti*-Diol-Containing Subunits. *Chem. Eur. J.* **2013**, *19*, 8088–8093.

[8] Alam, M; Wise, C.; Baxter, C. A.; Cleator, E.; Walkinshaw, A. Development of a Robust Procedure for the Copper-Catalyzed Ring-Opening of Epoxides with Grignard Reagents. *Org. Proc. Res. Dev.* **2012**, *16*, 435–441.

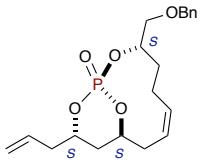
7.4 Hz, 2H, $H_2C$=CH-C$\underline{H_2}$CHO(P)$CH_2$, $H_2C$=CH-C$\underline{H_2}$CHO(P)$CH_2$), 2.23–2.09 (m, 2H, $H_2C$=CH-C$\underline{H_2}$-$CH_2$-CHO(P)$CH_2$OBn), 2.03–1.95 (m, 1H, $H_2C$=CHC$H_2$-CHO(P)C$\underline{H_a}H_b$CHO[P]), 1.89 (dqd, $J$ = 14.5, 3.8, 1.8 Hz, 1H, $H_2C$=CHC$H_2$-CHO(P)C$\underline{H_a}H_b$CHO[P]), 1.85–1.79 (m, 2H, $H_2C$=CH-$CH_2$-C$\underline{H_2}$-CHO(P)$CH_2$OBn);

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ ppm 138.0 (C), 137.4 (CH), 132.6 (CH), 132.3 (CH), 128.3 (2 x CH), 127.61 (2 x CH), 127.59 (CH), 118.9 ($CH_2$), 118.7 ($CH_2$), 115.2 ($CH_2$), 77.8 (d, $J_{CP}$ = 6.3 Hz, CH), 76.8 (d, $J_{CP}$ = 7.9 Hz, CH), 75.5 (d, $J_{CP}$ = 6.6 Hz, CH), 73.2 ($CH_2$), 71.6 (d, $J_{CP}$ = 4.0 Hz, $CH_2$), 39.9 (d, $J_{CP}$ = 7.3 Hz, $CH_2$), 39.1 (d, $J_{CP}$ = 3.9 Hz, $CH_2$), 33.1 (d, $J_{CP}$ = 6.7 Hz, $CH_2$), 31.4 (d, $J_{CP}$ = 5.0 Hz, $CH_2$), 29.2 ($CH_2$);

**$^{31}$P NMR (162 MHz, $CDCl_3$)** δ ppm –7.04 (dt, $J_{PH}$ = 13.7, 6.9 Hz);

**HRMS (TOF MS ES+)** calcd for $(C_{22}H_{31}O_5P)_2Na$ $(2M+Na)^+$ 835.3716; found 835.3748.

**(1*R*,3*S*,9*S*,11*S*,*Z*)-11-allyl-3-((benzyloxy)methyl)-2,12,13-trioxa-1-phosphabicyclo[7.3.1]tridec-6-ene 1-oxide (*trans*-2.12.5, *Z*-product [major]):**



*Z-trans*-**2.12.5**

Following General Procedure 2, triene **2.12.1** (40.0 mg, 0.0984 mmol) was exposed to G-I catalyst (6 mol %, over 7 hours) in refluxing $CH_2Cl_2$ to provide the corresponding bicyclic phosphates *trans*-**2.12.5** (22.8 mg, 0.0603 mmol, 61% combined yield) as a 2:1 mixture of *Z*:*E*-stereoisomers. Purification by flash chromatography provided clean *Z*-product (16.0 mg, 0.0422 mmol, 43%) as a colorless oil.

**FTIR (neat)**: 2924, 1452, 1277, 1105, 1022, 976, 930, 737, 698 $cm^{-1}$;

**Optical Rotation:** $[\alpha]_D = -40.5$ (*c* 0.83, $CHCl_3$);

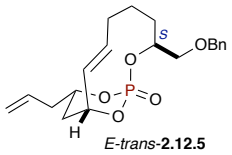
**$^1$H NMR (500 MHz, $CDCl_3$)** δ ppm 7.34 (d, *J* = 4.5 Hz, 4H, Aromatic C-H), 7.32–7.28 (m, 1H, Aromatic C-H), 5.80 (dddd, *J* = 17.2, 10.2, 7.9, 6.0 Hz, 1H, $CH_2$(P)OCHCH$_2$C<u>H</u>=CH$_2$), 5.63–5.53 (m, 2H, $CH_2$(P)OCHCH$_2$C<u>H</u>=C<u>H</u>CH$_2$), 5.22–5.14 (m, 2H, $CH_2$(P)OCHCH$_2$CH=C<u>H$_2$</u>), 4.92–4.86 (m, 1H, $CH_2$(P)OC<u>H</u>CH$_2$CH=CHCH$_2$), 4.66 (dtdd, *J* = 14.5, 7.2, 6.1, 3.7 Hz, 1H, $CH_2$(P)OC<u>H</u>CH$_2$CH=CH$_2$), 4.58 (d, *J* = 11.9 Hz, 1H, –OC<u>H$_a$</u>H$_b$Ph), 4.55 (d, *J* = 11.9 Hz, 1H, –OCH$_a$<u>H$_b$</u>Ph), 4.24 (tdd, *J* = 9.1, 7.5, 4.5 Hz, 1H, -HC=CHCH$_2$CH$_2$C<u>H</u>O(P)CH$_2$OBn), 3.66 (dd, *J* = 10.1, 5.7 Hz, 1H, -CHO(P)C<u>H$_a$</u>H$_b$OBn), 3.50 (dd, *J* = 10.1, 6.4 Hz, 1H, -CHO(P)CH$_a$<u>H$_b$</u>OBn), 2.80–2.70 (m, 3H, $CH_2$(P)OCHC<u>H$_a$</u>H$_b$CH=CH$_2$, $CH_2$(P)OCHC<u>H$_a$</u>H$_b$CH=CHC<u>H$_a$</u>H$_b$-), 2.49 (dt, *J* = 14.8, 7.7 Hz, 1H, $CH_2$(P)OCHCH$_a$<u>H$_b$</u>CH=CH$_2$), 2.28 (d, *J* = 18.2 Hz, 1H, $CH_2$(P)OCHCH$_a$<u>H$_b$</u>CH=CHCH$_2$-), 2.16–2.05 (m, 2H, $CH_2$(P)OCHCH$_2$CH=CHCH$_a$<u>H$_b$</u>CH$_2$, H$_2$C=CHCH$_2$-CHO(P)C<u>H$_a$</u>H$_b$CHO[P]), 1.96–1.87 (m, 1H, H$_2$C=CHCH$_2$-CHO(P)CH$_a$<u>H$_b$</u>CHO[P]), 1.87–1.80 (m, 2H, $CH_2$(P)OCHCH$_2$CH=CHCH$_2$C<u>H$_2$</u>CHO[P]);

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ ppm 138.0 (C), 135.7 (CH), 132.3 (CH), 128.3 (2 x CH), 127.66 (2 x CH), 127.62 (CH), 123.8 (CH), 119.0 ($CH_2$), 78.0 (d, $J_{CP}$ = 6.3 Hz, CH), 76.5 (d, $J_{CP}$ = 8.3 Hz, 2 x CH), 73.5 ($CH_2$), 72.7 (d, $J_{CP}$ = 5.9 Hz, $CH_2$), 39.0 (d, $J_{CP}$ = 3.5 Hz, $CH_2$), 32.1 (d, $J_{CP}$ = 4.5 Hz, $CH_2$), 31.3 (d, $J_{CP}$ = 3.0 Hz, $CH_2$), 31.1 ($CH_2$), 23.8 ($CH_2$);

**$^{31}$P NMR (162 MHz, $CDCl_3$)** δ ppm –14.14 (dt, $J_{PH}$ = 13.9, 7.0 Hz);

**HRMS (TOF MS ES+)** calcd for $(C_{20}H_{27}O_5P)_2Na$ $(2M+Na)^+$ 779.3090; found 779.3094.

**(1*R*,3*S*,9*S*,11*S*,*E*)-11-allyl-3-((benzyloxy)methyl)-2,12,13-trioxa-1-phosphabicyclo[7.3.1]tridec-6-ene 1-oxide** (*E-trans*-**2.12.5**, *E*-product [minor]):



*E-trans*-**2.12.5**

Following General Procedure 2, triene **2.12.1** (40.0 mg, 0.0984 mmol) was exposed to G-I catalyst (6 mol %, over 7 hours) in refluxing $CH_2Cl_2$ to provide the corresponding bicyclic phosphates *trans*-**2.12.5** (22.8 mg, 0.0603 mmol, 61% combined yield) as a 2:1 mixture of *Z*:*E*-stereoisomers. Purification by flash chromatography provided clean *E*-product (6.8 mg, 0.0180 mmol, 18%) as a colorless oil.

**FTIR (neat)**: 2924, 2853, 1452, 1364, 1273, 1097, 1024, 982, 932, 698 $cm^{-1}$;

**Optical Rotation** $[\alpha]_D = -77.6$ (*c* 0.21, $CHCl_3$);

**$^1$H NMR (500 MHz, $CDCl_3$)** δ ppm 7.35 (d, *J* = 4.4 Hz, 4H, Aromatic C-H), 7.32–7.28 (m, 1H, Aromatic C-H), 5.87–5.71 (m, 2H, $CH_2$(P)OCHCH$_2$C<u>H</u>=CH$_2$, $CH_2$(P)OCHCH$_2$CH=C<u>H</u>CH$_2$), 5.50 (dddd, *J* = 15.3, 10.1, 5.5, 1.7 Hz, 1H, $CH_2$(P)OCHCH$_2$C<u>H</u>=CHCH$_2$), 5.24–5.15 (m, 2H, $CH_2$(P)OCHCH$_2$CH=C<u>H</u>$_2$), 4.94–4.84 (m, 1H, $CH_2$(P)OC<u>H</u>CH$_2$CH=CHCH$_2$), 4.69–4.51 (m, 3H, $CH_2$(P)OC<u>H</u>CH$_2$CH=CH$_2$, -OC<u>H</u>$_2$Ph), 4.14 (dddd, *J* = 13.8, 9.8, 6.5, 1.1 Hz, 1H, -HC=CHCH$_2$CH$_2$C<u>H</u>O(P)CH$_2$OBn), 3.66 (dd, *J* = 9.7, 5.3 Hz, 1H, -HC=CHCH$_2$CH$_2$CHO(P)C<u>H$_a$</u>H$_b$OBn), 3.46 (dd, *J* = 9.7, 7.4 Hz, 1H, HC=CHCH$_2$CH$_2$CHO(P)CH$_a$<u>H$_b$</u>OBn), 2.72 (dddt, *J* = 14.5, 7.4, 6.1, 1.5 Hz, 1H, $CH_2$(P)OCHC<u>H$_a$</u>H$_b$CH=CH$_2$), 2.63 (ddd, *J* = 14.5, 10.1, 4.9 Hz, 1H, $CH_2$(P)OCHC<u>H$_a$</u>H$_b$CH=CHCH$_2$), 2.52–2.43 (m, 2H, $CH_2$(P)OCHCH$_a$<u>H$_b$</u>CH=CHCH$_2$, $CH_2$(P)OCHCH$_2$CH=CHC<u>H$_a$</u>H$_b$CH$_2$), 2.17–2.11 (m, 1H, $CH_2$(P)OCHCH$_a$<u>H$_b$</u>CH=CHCH$_2$), 2.10–1.92 (m, 4H,

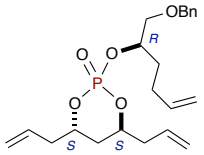
$CH_2(P)OCHCH_2CH{=}CHCH_a\underline{H}_bC\underline{H}_aH_bCHO[P]CH_2OBn$, $H_2C{=}CHCH_2$-$CHO(P)C\underline{H}_2CHO[P]$), 1.75 (dddd, $J$ = 15.1, 13.0, 8.5, 4.5 Hz, 1H, $CH_2(P)OCHCH_2CH{=}CHCH_2CH_a\underline{H}_bCHO[P]CH_2OBn$);

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ ppm 138.8 (CH), 138.0 (C), 132.2 (CH), 128.4 (2 x CH), 127.8 (2 x CH), 127.7 (CH), 122.1 (CH), 119.1 ($CH_2$), 78.8 (d, $J_{CP}$ = 9.5 Hz, CH), 78.0 (d, $J_{CP}$ = 6.4 Hz, CH), 77.8 (d, $J_{CP}$ = 9.5 Hz, CH), 73.6 ($CH_2$), 72.6 (d, $J_{CP}$ = 1.7 Hz, $CH_2$), 39.3 (d, $J_{CP}$ = 3.7 Hz, $CH_2$), 36.8 ($CH_2$), 32.0 ($CH_2$), 31.9 (d, $J_{CP}$ = 9.5 Hz, $CH_2$), 31.0 (d, $J_{CP}$ = 7.5 Hz, $CH_2$);

**$^{31}$P NMR (162 MHz, $CDCl_3$)** δ ppm –15.94 (d, $J_{PH}$ = 12.8 Hz);

**HRMS (TOF MS ES+)** calcd for $(C_{20}H_{27}O_5P)_2Na$ $(2M+Na)^+$ 779.3090; found 779.3069.

**(4*S*,6*S*)-4,6-diallyl-2-(((*R*)-1-(benzyloxy)hex-5-en-2-yl)oxy)-1,3,2-dioxaphosphinane 2-oxide** (**2.12.2**):



(*R*,*S*,*S*)-**2.12.2**

Following General Procedure 1, monochlorophosphate (*S,S*)-**2.12.3** (0.182 g, 0.769 mmol) and alcohol (*R*)-**2.12.4**[9] (0.145 g, 0.705 mmol) were converted into **2.12.2** (0.175 g, 0.430 mmol, 67%) which was isolated as a colorless oil.

**FTIR (neat)**: 2930, 2862, 1452, 1366, 1286, 1097, 1078, 997, 976, 916, 816, 739, 629, 550 $cm^{-1}$;

[9] Takano, S.; Moriya, M.; Iwabuchi, Y. Ogasawara, K. Concise Synthesis of $C_2$-Symmetric *Trans*-2,5-Dioxymethylpyrrolidine Derivatives by Novel Cyclization. *Tetrahedron Lett.* **1989**, *30*, 3805–3806.

**Optical Rotation:** $[\alpha]_D = -38.2$ (*c* 0.60, $CHCl_3$);

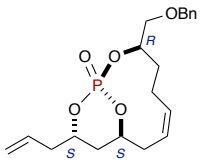
**$^1$H NMR (500 MHz, $CDCl_3$)** δ ppm 7.38–7.28 (m, 5H, Aromatic C-H), 5.86–5.63 (m, 3H, $H_2C$=C<u>H</u>-$CH_2$-$CH_2$-CHO(P)$CH_2$OBn, $H_2C$=C<u>H</u>-$CH_2$-$CH_2$-CHO(P)$CH_2$OBn), 5.15–5.10 (m, 3H, <u>$H_2$</u>C=CH-$CH_2$CHO(P)$CH_2$, <u>$H_a$</u>$H_b$C=CH-$CH_2$CHO(P)$CH_2$), 5.08 (d, *J* = 1.4 Hz, 1H, $H_a$<u>$H_b$</u>C=CH-$CH_2$CHO(P)$CH_2$), 5.04 (dq, *J* = 17.1, 1.7 Hz, 1H, <u>$H_a$</u>$H_b$C=CH-$CH_2$-$CH_2$-CHO(P)$CH_2$OBn), 4.98 (dq, *J* = 10.2, 1.4 Hz, 1H, $H_a$<u>$H_b$</u>C=CH-$CH_2$-$CH_2$-CHO(P)$CH_2$OBn), 4.66–4.47 (m, 5H, $H_2C$=CH$CH_2$-C<u>H</u>O(P)$CH_2$, $H_2C$=CH$CH_2$-C<u>H</u>O(P)$CH_2$, C<u>H</u>O(P)$CH_2$OBn, OC<u>$H_2$</u>Ph), 3.66–3.53 (m, 2H, CHO(P)C<u>$H_2$</u>OBn), 2.68 (dddt, *J* = 13.5, 7.5, 6.3, 1.5 Hz, 1H, $H_2C$=CH-C<u>$H_a$</u>$H_b$CHO(P)$CH_2$), 2.49–2.43 (m, 1H, $H_2C$=CH-C<u>$H_a$</u>$H_b$CHO(P)$CH_2$), 2.43–2.35 (m, 1H, $H_2C$=CH-$CH_a$<u>$H_b$</u>CHO(P)$CH_2$), 2.34–2.27 (m, 1H, $H_2C$=CH-$CH_a$<u>$H_b$</u>CHO(P)$CH_2$), 2.17 (tddd, *J* = 7.8, 6.5, 5.1, 1.4 Hz, 2H, $H_2C$=CH-C<u>$H_2$</u>-$CH_2$-CHO(P)$CH_2$OBn), 1.97 (dddd, *J* = 14.8, 8.6, 5.0, 1.4 Hz, 1H, $H_2C$=CH$CH_2$-CHO(P)C<u>$H_a$</u>$H_b$CHO[P]), 1.91–1.76 (m, 3H, $H_2C$=CH$CH_2$-CHO(P)$CH_a$<u>$H_b$</u>CHO[P], $H_2C$=CH-$CH_2$-C<u>$H_2$</u>-CHO(P)$CH_2$OBn);

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ ppm 137.9 (C), 137.5 (CH), 132.8 (CH), 132.3 (CH), 128.4 (2 x CH), 127.7 (CH), 127.6 (2 x CH), 118.7 ($CH_2$), 118.6 ($CH_2$), 115.2 ($CH_2$), 77.4 (d, $J_{CP}$ = 2.4 Hz, CH), 77.4 (d, $J_{CP}$ = 3.3 Hz, CH), 75.0 (d, $J_{CP}$ = 6.7 Hz, CH), 73.2 ($CH_2$), 71.8 (d, $J_{CP}$ = 4.2 Hz, $CH_2$), 40.0 (d, $J_{CP}$ = 7.8 Hz, $CH_2$), 38.9 (d, $J_{CP}$ = 3.2 Hz, $CH_2$), 33.0 (d, $J_{CP}$ = 6.8 Hz, $CH_2$), 31.5 (d, $J_{CP}$ = 4.9 Hz, $CH_2$), 29.2 ($CH_2$);

**$^{31}$P NMR (162 MHz, $CDCl_3$)** δ ppm –7.18 (s);

**HRMS (TOF MS ES+)** calcd for $(C_{22}H_{31}O_5P)_2Na$ $(2M+Na)^+$ 835.3716; found 835.3719.

**(1*R*,3*R*,9*S*,11*S*,*Z*)-11-allyl-3-((benzyloxy)methyl)-2,12,13-trioxa-1-phosphabicyclo[7.3.1]tridec-6-ene 1-oxide** (*cis*-**2.12.6**):




*cis*-**2.12.6**

Following General Procedure 2, triene **2.12.2** (30.0 mg, 0.0738 mmol) was exposed to G-I catalyst (3 mol %, over 4 hours) in refluxing $CH_2Cl_2$ to provide the corresponding bicyclic phosphate *cis*-**2.12.6** (24.6 mg, 0.0650 mmol, 88%) as a colorless oil.

**FTIR (neat):** 2924, 2858, 1454, 1364, 1285, 1096, 978, 735, 698, 559 $cm^{-1}$;

**Optical Rotation** $[\alpha]_D = -14.9$ (*c* 1.01, $CHCl_3$);

**$^1$H NMR (500 MHz, $CDCl_3$)** δ ppm 7.33 (d, *J* = 4.4 Hz, 4H, Aromatic C-H), 7.30–7.25 (m, 1H, Aromatic C-H), 5.83 (ddt, *J* = 16.6, 10.8, 7.1 Hz, 1H, $CH_2(P)OCHCH_2C\underline{H}=CH_2$), 5.63–5.53 (m, 2H, $CH_2(P)OCHCH_2C\underline{H}=C\underline{H}CH_2$), 5.18 (dd, *J* = 6.8, 1.5 Hz, 1H, $CH_2(P)OCHCH_2CH=C\underline{H}_aH_b$), 5.15 (d, *J* = 1.4 Hz, 1H, $CH_2(P)OCHCH_2CH=CH_a\underline{H}_b$), 4.79 (dtd, *J* = 12.1, 6.2, 1.9 Hz, 1H, $CH_2(P)OC\underline{H}CH_2CH=CHCH_2$), 4.72–4.60 (m, 2H, $CH_2(P)OC\underline{H}CH_2CH=CH_2$, $-OC\underline{H}_aH_bPh$), 4.52 (d, *J* = 12.0 Hz, 1H, $-OCH_a\underline{H}_bPh$), 4.37 (dtt, *J* = 12.0, 5.9, 2.9 Hz, 1H, -HC=CHCH$_2$CH$_2$C$\underline{H}$O(P)CH$_2$OBn), 3.94 (dd, *J* = 10.2, 5.7 Hz, 1H, -CHO(P)C$\underline{H}_a$H$_b$OBn), 3.79 (dd, *J* = 10.1, 2.7 Hz, 1H, -CHO(P)CH$_a\underline{H}_b$OBn), 3.23 (q, *J* = 12.5, 11.7 Hz, 1H, $CH_2(P)OCHC\underline{H}_aH_bCH=CHCH_2$), 2.62 (tq, *J* = 13.1, 10.8, 4.9 Hz, 1H, $CH_2(P)OCHCH_2CH=CHC\underline{H}_aH_bCH_2$), 2.53 (dtd, *J* = 14.2, 6.4, 1.5 Hz, 1H, $CH_2(P)OCHC\underline{H}_aH_bCH=CH_2$), 2.45–2.35 (m, 1H, $CH_2(P)OCHCH_a\underline{H}_bCH=CH_2$), 2.25 (ddd, *J* = 14.6, 11.9, 5.6 Hz, 1H, $H_2C=CHCH_2$-CHO(P)C$\underline{H}_a$H$_b$CHO[P]), 2.09 (dddd, *J* = 14.6, 11.8, 4.8, 2.8 Hz, 1H, $CH_2(P)OCHCH_2CH=CHCH_2C\underline{H}_aH_bCHO[P]$), 2.01 (d, *J* =

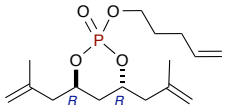
13.1 Hz, 1H, $CH_2$(P)OCHCH$_2$CH=CHCH$_a$$\underline{H}_b$CH$_2$), 1.94 (d, *J* = 14.0 Hz, 1H, $CH_2$(P)OCHCH$_a$$\underline{H}_b$CH=CHCH$_2$), 1.80–1.74 (m, 1H, $CH_2$(P)OCHCH$_2$CH=CHCH$_2$CH$_a$$\underline{H}_b$CHO[P]), 1.70 (dq, *J* = 14.7, 1.9 Hz, 1H, $H_2C$=CHCH$_2$-CHO(P)CH$_a$$\underline{H}_b$CHO[P]);

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ ppm 138.3 (C), 131.9 (CH), 130.2 (CH), 128.3 (2 x CH), 127.7 (2 x CH), 127.5 (CH), 126.0 (CH), 119.1 ($CH_2$), 76.9 (d, $J_{CP}$ = 7.7 Hz, CH), 75.7 (d, $J_{CP}$ = 7.3 Hz, CH), 74.7 (d, $J_{CP}$ = 2.7 Hz, CH), 73.5 ($CH_2$), 71.9 ($CH_2$), 40.6 (d, $J_{CP}$ = 9.0 Hz, $CH_2$), 34.3 (d, $J_{CP}$ = 6.9 Hz, $CH_2$), 31.5 ($CH_2$), 29.8 (d, $J_{CP}$ = 9.6 Hz, $CH_2$), 21.9 ($CH_2$);

**$^{31}$P NMR (162 MHz, $CDCl_3$)** δ ppm –9.76 (d, $J_{PH}$ = 23.5 Hz);

**HRMS (TOF MS ES+)** calcd for $(C_{20}H_{27}O_5P)_2Na$ $(2M+Na)^+$ 779.3090; found 779.3095.

**(4*R*,6*R*)-4,6-bis(2-methylallyl)-2-(pent-4-en-1-yloxy)-1,3,2-dioxaphosphinane 2-oxide (2.13.1)**:



(*R,R*)-**2.13.1**

Following General Procedure 1, (*R,R*)-monochlorophosphate **2.13.2**[7] (0.145 g, 0.548 mmol) and 4-penten-1-ol (43.2 mg, 0.502 mmol) were converted to phosphate triene **2.13.1** (0.115 g, 0.366 mmol, 80%) which was isolated as a colorless oil.

**FTIR (neat):** 2966, 2939, 1445, 1377, 1288.4, 1011, 970, 893, 814, 799, 542 $cm^{-1}$;

**Optical Rotation** $[\alpha]_D$ = +44.1 (*c* 0.88, $CHCl_3$);

**$^1$H NMR (500 MHz, $CDCl_3$)** δ ppm 5.80 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H, (P)OCH$_2$CH$_2$CH$_2$C$\underline{H}$=CH$_2$), 5.05 (dq, *J* = 17.2, 1.7 Hz, 1H,

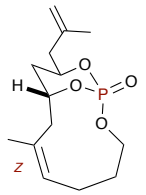
(P)OCH$_2$CH$_2$CH$_2$CH=C$\underline{H}_a$H$_b$), 5.00 (dq, *J* = 10.2, 1.5 Hz, 1H, (P)OCH$_2$CH$_2$CH$_2$CH=CH$_a\underline{H}_b$), 4.87 (q, *J* = 1.5 Hz, 2H, $\underline{H}_a$H$_b$C=C(CH$_3$)-CH$_2$CHO(P)CH$_2$, $\underline{H}_a$H$_b$C=C(CH$_3$)-CH$_2$CHO(P)CH$_2$), 4.78 (d, *J* = 5.94 Hz, 2H, H$_a\underline{H}_b$C=C(CH$_3$)-CH$_2$CHO(P)CH$_2$, H$_a\underline{H}_b$C=C(CH$_3$)-CH$_2$CHO(P)CH$_2$), 4.77–4.71 (m, 1H, H$_2$C=C(CH$_3$)-CH$_2$C$\underline{H}$O(P)CH$_2$), 4.63 (dtdd, *J* = 8.7, 6.8, 5.2, 3.6 Hz, 1H, H$_2$C=C(CH$_3$)-CH$_2$C$\underline{H}$O(P)CH$_2$), 4.10 (q, *J* = 6.7 Hz, 2H, (P)OC$\underline{H}_2$CH$_2$CH$_2$CH=CH$_2$), 2.62 (dd, *J* = 14.2, 7.0 Hz, 1H, H$_2$C=C(CH$_3$)-C$\underline{H}_a$H$_b$CHO(P)CH$_2$), 2.56 (dd, *J* = 14.3, 6.9 Hz, 1H, H$_2$C=C(CH$_3$)-C$\underline{H}_a$H$_b$CHO(P)CH$_2$), 2.41–2.30 (m, 2H, H$_2$C=C(CH$_3$)-CH$_a\underline{H}_b$CHO(P)CH$_2$, H$_2$C=C(CH$_3$)-CH$_a\underline{H}_b$CHO(P)CH$_2$), 2.16 (dt, *J* = 8.0, 6.7 Hz, 2H, (P)OCH$_2$CH$_2$C$\underline{H}_2$CH=CH$_2$), 2.01 (dddd, *J* = 14.8, 8.5, 5.0, 1.4 Hz, 1H, H$_2$C=C(CH$_3$)CH$_2$-CHO(P)C$\underline{H}_a$H$_b$CHO[P]), 1.87 (dddd, *J* = 14.7, 5.1, 3.5, 1.8 Hz, 1H, H$_2$C=C(CH$_3$)CH$_2$-CHO(P)CH$_a\underline{H}_b$CHO[P]), 1.83–1.78 (m, 2H, (P)OCH$_2$C$\underline{H}_2$CH$_2$CH=CH$_2$), 1.76 (dd, *J* = 5.3, 1.1 Hz, 6H, H$_2$C=C(C$\underline{H}_3$)-CH$_2$CHO(P)CH$_2$);

**$^{13}$C NMR (126 MHz, CDCl$_3$)** δ ppm 140.3 (C), 140.2 (C), 137.2 (CH), 115.4 (CH$_2$), 114.2 (2 x CH$_2$), 75.8 (d, $J_{CP}$ = 6.8 Hz, CH), 74.5 (d, $J_{CP}$ = 6.5 Hz, CH), 67.2 (d, $J_{CP}$ = 5.9 Hz, CH$_2$), 43.7 (d, $J_{CP}$ = 7.2 Hz, CH$_2$), 42.7 (d, $J_{CP}$ = 3.2 Hz, CH$_2$), 33.4 (d, $J_{CP}$ = 6.9 Hz, CH$_2$), 29.6 (CH$_2$), 29.5 (d, $J_{CP}$ = 6.7 Hz, CH$_2$), 22.6 (CH$_3$), 22.3 (CH$_3$);

**$^{31}$P NMR (162 MHz, CDCl$_3$)** δ ppm –6.71 (d, $J_{PH}$ = 7.2 Hz);

**HRMS (TOF MS ES+)** calcd for (C$_{16}$H$_{27}$O$_4$P)$_2$Na (2M+Na)$^+$ 651.3192; found 651.3194.

**(1*S*,9*R*,11*R*,*Z*)-7-methyl-11-(2-methylallyl)-2,12,13-trioxa-1-phosphabicyclo[7.3.1]tridec-6-ene 1-oxide** (**2.13.3**):




($S_P$,*R*,*R*)-**2.13.3**

Following General Procedure 2, triene **2.13.1** (20.0 mg, 0.0636 mmol) was exposed to G-II catalyst (2 mol %, over 2 hours) in refluxing $CH_2Cl_2$ to provide the corresponding bicyclic phosphate **2.13.3** (15.8 mg, 0.0552 mmol, 87%) as a white, crystalline solid, which was recrystallized via vapor-diffusion method (EtOAc:Hexanes) to obtain X-ray quality crystals for X-ray crystallographic analysis (which confirmed stereochemical olefin assignment as *Z*).[10]

**FTIR (neat)**: 2964, 2926, 2860, 1435, 1379, 1279, 1221, 1101, 1086, 1069, 1024, 984, 953, 914, 843, 791, 764, 546 $cm^{-1}$;

**Optical Rotation** $[\alpha]_D = -18.7$ (*c* 0.70, $CHCl_3$);

**$^1$H NMR (500 MHz, $CDCl_3$)** δ ppm 5.25 (ddt, *J* = 10.6, 3.4, 1.6 Hz, 1H, $CH_2$(P)OCHC$H_2$C($CH_3$)=C$\underline{H}$C$H_2$), 4.91–4.79 (m, 4H, $\underline{H_2}$C=C($CH_3$)$CH_2$-CHO(P)$CH_2$, $H_2$C=C($CH_3$)$CH_2$-C$\underline{H}$O(P)$CH_2$C$\underline{H}$O[P]), 4.04 (dt, *J* = 7.9, 1.8 Hz, 2H, (P)OC$\underline{H_2}$$CH_2$$CH_2$CH=C($CH_3$)$CH_2$), 3.35 (t, *J* = 13.5 Hz, 1H, $CH_2$(P)OCHC$\underline{H_a}H_b$C($CH_3$)=C$H$C$H_2$), 2.57–2.44 (m, 2H, $H_2$C=C($CH_3$)C$\underline{H_a}H_b$-CHO(P)$CH_2$, $CH_2$(P)OCHC$H_2$C($CH_3$)=CHC$\underline{H_a}H_b$$CH_2$), 2.30 (ddd, *J* = 14.3, 6.4, 2.8 Hz, 1H, $H_2$C=C($CH_3$)C$H_a\underline{H_b}$-CHO(P)$CH_2$), 2.22 (ddd, *J* = 14.6, 11.8, 5.6 Hz, 1H,

[ 10 ] All X-ray crystallographic data has been submitted to the Cambridge Crystallographic Data Centre, and the structures were assigned the following deposition numbers: **2.13.3** (1431827) and *trans*-**2.16.6** (1431826).

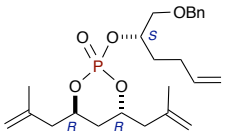
$H_2C$=C($CH_3$)$CH_2$-CHO(P)C$\underline{H}_a$$H_b$CHO[P]), 1.99 (ddt, *J* = 14.2, 9.8, 4.3 Hz, 2H, $CH_2$(P)OCHC$H_2$C($CH_3$)=CHC$H_a$$\underline{H}_b$$CH_2$, (P)OC$H_2$C$\underline{H}_a$$H_b$$CH_2$CH=C($CH_3$)$CH_2$), 1.80 (s, 3H, $CH_2$(P)OCHC$H_2$C(C$\underline{H}_3$)=C$HCH_2$), 1.79 (dd, *J* = 1.1, 1.1 Hz, 3H, $H_2C$=C(C$\underline{H}_3$)$CH_2$-CHO(P)$CH_2$), 1.75 (dd, *J* = 14.1, 2.3 Hz, 1H, $CH_2$(P)OCHC$H_a$$\underline{H}_b$C($CH_3$)=C$HCH_2$), 1.70 (d, *J* = 14.7 Hz, 1H, $H_2C$=C($CH_3$)$CH_2$-CHO(P)C$H_a$$\underline{H}_b$CHO[P]), 1.51 (dddd, *J* = 17.2, 10.4, 5.4, 3.2 Hz, 1H, (P)OC$H_2$C$H_a$$\underline{H}_b$$CH_2$CH=C($CH_3$)$CH_2$);

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ ppm 140.0 (C), 132.8 (C), 125.0 (CH), 114.3 ($CH_2$), 75.2 (d, $J_{CP}$ = 7.5 Hz, CH), 74.8 (d, $J_{CP}$ = 7.0 Hz, CH), 64.2 (d, $J_{CP}$ = 5.0 Hz, $CH_2$), 44.4 (d, $J_{CP}$ = 9.1 Hz, $CH_2$), 34.9 ($CH_2$), 34.7 (d, $J_{CP}$ = 6.7 Hz, $CH_2$), 26.8 (d, $J_{CP}$ = 10.1 Hz, $CH_2$), 22.9 ($CH_3$), 22.5 ($CH_2$), 22.0 ($CH_3$);

**$^{31}$P NMR (162 MHz, $CDCl_3$)** δ ppm –8.16 (d, $J_{PH}$ = 23.5 Hz);

**HRMS (TOF MS ES+)** calcd for $(C_{14}H_{23}O_4P)_2Na$ $(2M+Na)^+$ 595.2566; found 595.2538.

**(4*R*,6*R*)-2-(((*S*)-1-(benzyloxy)hex-5-en-2-yl)oxy)-4,6-bis(2-methylallyl)-1,3,2-dioxaphosphinane 2-oxide** (**2.13.4**):



(*R,R,S*)-**2.13.4**

Following General Procedure 1, monochlorophosphate (*R,R*)-**2.13.2** (0.180 g, 0.680 mmol) and alcohol (*S*)-**2.12.4** (0.129 g, 0.623 mmol) were converted into phosphate triene **2.13.4** (0.194 g, 0.447 mmol, 79%) which was isolated as a colorless oil.

**FTIR (neat):** 2964, 2936, 2860, 1454, 1377, 1367, 1288, 1101, 1072, 990, 895, 814, 737, 698, 552 $cm^{-1}$;

**Optical Rotation** $[\alpha]_D$ = +36.5 (*c* 1.97, $CHCl_3$);

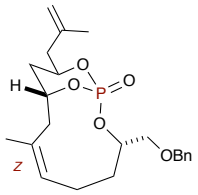
**$^{1}$H NMR (500 MHz, $CDCl_3$)** δ ppm 7.36–7.27 (m, 5H, Aromatic C-H), 5.80 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H, $H_2C$=C<u>H</u>-$CH_2$-$CH_2$-CHO(P)$CH_2$OBn), 5.03 (dd, *J* = 17.2, 1.7 Hz, 1H, <u>H</u>$_a$H$_b$C=CH-$CH_2$-$CH_2$-CHO(P)$CH_2$OBn), 4.97 (dd, *J* = 10.2, 1.7 Hz, 1H, H$_a$<u>H</u>$_b$C=CH-$CH_2$-$CH_2$-CHO(P)$CH_2$OBn), 4.85 (d, *J* = 1.7 Hz, 1H, <u>H</u>$_a$H$_b$C=C($CH_3$)-$CH_2$CHO(P)$CH_2$), 4.82 (dd, *J* = 1.7, 1.7 Hz, 1H, <u>H</u>$_a$H$_b$C=C($CH_3$)-$CH_2$CHO(P)$CH_2$), 4.76–4.74 (m, 2H, H$_a$<u>H</u>$_b$C=C($CH_3$)-$CH_2$CHO(P)$CH_2$, H$_a$<u>H</u>$_b$C=C($CH_3$)-$CH_2$CHO(P)$CH_2$), 4.73–4.65 (m, 2H, $H_2C$=C($CH_3$)-$CH_2$C<u>H</u>O(P)$CH_2$, $H_2C$=C($CH_3$)-$CH_2$C<u>H</u>O(P)$CH_2$), 4.63–4.51 (m, 3H, $H_2C$=CH-$CH_2$-$CH_2$-C<u>H</u>O(P)$CH_2$OBn, OC<u>H</u>$_2$Ph), 3.62–3.55 (m, 2H, $H_2C$=CH-$CH_2$-$CH_2$-CHO(P)C<u>H</u>$_2$OBn), 2.67–2.61 (m, 1H, $H_2C$=C($CH_3$)-C<u>H</u>$_a$H$_b$CHO(P)$CH_2$), 2.49 (dd, *J* = 14.1, 6.5 Hz, 1H, $H_2C$=C($CH_3$)-C<u>H</u>$_a$H$_b$CHO(P)$CH_2$), 2.36 (dd, *J* = 14.2, 7.4 Hz, 1H, $H_2C$=C($CH_3$)-CH$_a$<u>H</u>$_b$CHO(P)$CH_2$), 2.29 (ddt, *J* = 14.1, 7.3, 1.2 Hz, 1H, $H_2C$=C($CH_3$)-CH$_a$<u>H</u>$_b$CHO(P)$CH_2$), 2.16 (dddd, *J* = 15.6, 9.1, 7.1, 4.0 Hz, 2H, $H_2C$=CH-C<u>H</u>$_2$-$CH_2$-CHO(P)$CH_2$OBn), 1.96 (dddd, *J* = 14.5, 8.2, 4.9, 1.4 Hz, 1H, $H_2C$=C($CH_3$)$CH_2$-CHO(P)C<u>H</u>$_a$H$_b$CHO[P]), 1.90–1.76 (m, 3H, $H_2C$=C($CH_3$)$CH_2$-CHO(P)CH$_a$<u>H</u>$_b$CHO[P], $H_2C$=CH-$CH_2$-C<u>H</u>$_2$-CHO(P)$CH_2$OBn), 1.74 (t, *J* = 1.0 Hz, 3H, $H_2C$=C(C<u>H</u>$_3$)-$CH_2$CHO(P)$CH_2$), 1.69 (t, *J* = 1.1 Hz, 3H, $H_2C$=C(C<u>H</u>$_3$)-$CH_2$CHO(P)$CH_2$);

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ ppm 140.4 (C), 140.3 (C), 137.8(C), 137.5 (CH), 128.3 (2 x CH), 127.7 (CH), 127.6 (2 x CH), 115.1 ($CH_2$), 114.1 (2 x $CH_2$), 77.4 (d, $J_{CP}$ = 6.2 Hz, CH), 76.0 (d, $J_{CP}$ = 6.8 Hz, CH), 74.3 (d, $J_{CP}$ = 6.6 Hz, CH), 73.1 ($CH_2$), 71.7 (d, $J_{CP}$ = 4.2 Hz, $CH_2$), 43.7 (d, $J_{CP}$ = 7.4 Hz, $CH_2$), 42.8 (d, $J_{CP}$ = 3.5 Hz, $CH_2$), 33.3 (d, $J_{CP}$ = 6.9 Hz, $CH_2$), 31.4 (d, $J_{CP}$ = 4.7 Hz, $CH_2$), 29.1 ($CH_2$), 22.6 ($CH_3$), 22.3 ($CH_3$);

**$^{31}$P NMR (162 MHz, $CDCl_3$)** δ ppm –7.13 (m);[11]

**HRMS (TOF MS ES+)** calcd for $(C_{24}H_{35}O_5P)_2Na$ $(2M+Na)^+$ 891.4342; found 891.4326.

**(1*S*,3*S*,9*R*,11*R*,*Z*)-3-((benzyloxy)methyl)-7-methyl-11-(2-methylallyl)-2,12,13-trioxa-1-phosphabicyclo[7.3.1]tridec-6-ene 1-oxide** (*cis*-**2.13.6**):




*cis*-**2.13.6**

Following General Procedure 2, triene **2.13.4** (30.0 mg, 0.0690 mmol) was exposed to G-II catalyst (2 mol %, over 2 hours) in refluxing $CH_2Cl_2$ to provide the corresponding bicyclic phosphate *cis*-**2.13.6** (22.6 mg, 0.0556 mmol, 81%) as a colorless oil.

**FTIR (neat)**: 2966, 2920, 1454, 1377, 1285, 1099, 1072, 980, 916, 793, 698, 546 $cm^{-1}$;

**Optical Rotation:** $[\alpha]_D$ = –4.6 (*c* 0.67, $CHCl_3$);

**$^1$H NMR (500 MHz, $CDCl_3$)** δ ppm 7.34 (d, *J* = 4.5 Hz, 4H, Aromatic C-H), 7.30–7.25 (m, 1H, Aromatic C-H), 5.28 (ddt, *J* = 10.6, 3.2, 1.5 Hz, 1H, $CH_2$(P)OCHC$H_2$C($CH_3$)=C$\underline{H}$C$H_2$), 4.93–4.78 (m, 4H, $\underline{H_2}$C=C($CH_3$)$CH_2$-CHO(P)$CH_2$, $H_2$C=C($CH_3$)$CH_2$-C$\underline{H}$O(P)$CH_2$C$\underline{H}$O[P]), 4.62 (d, *J* = 12.0 Hz, 1H, -OC$\underline{H_a}H_b$Ph), 4.53 (d, *J* = 12.0 Hz, 1H, -OC$H_a\underline{H_b}$Ph), 4.36 (dtt, *J* = 12.0, 5.9, 2.8 Hz, 1H, $CH_2$($CH_3$)C=CHC$H_2$C$H_2$C$\underline{H}$O(P)$CH_2$OBn), 3.92 (dd, *J* = 10.2, 5.8 Hz, 1H, $CH_2$CHO(P)C$\underline{H_a}H_b$OBn), 3.80 (dd, *J* = 10.1, 2.7 Hz, 1H, $CH_2$CHO(P)C$H_a\underline{H_b}$OBn), 3.32 (t, *J* = 13.5 Hz, 1H, $CH_2$(P)OCHC$\underline{H_a}H_b$C($CH_3$)=C$H_2$), 2.52 (tdd, *J* = 16.9, 9.3, 4.4 Hz,

[11] Due to complex PH coupling, some $^{31}$P NMR for new compounds appear as a single peak with complex splitting; this multiplet collapses to a singlet in proton-decoupled $^{31}$P $\{^1H\}$ NMR.

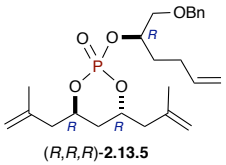
2H, $CH_2(CH_3)C=CHC\underline{H}_aH_bCH_2CHO(P)CH_2OBn$, $H_2C=C(CH_3)C\underline{H}_aH_b$-$CHO(P)CH_2$), 2.32 (ddd, *J* = 14.3, 7.1, 2.2 Hz, 1H, $H_2C=C(CH_3)CH_a\underline{H}_b$-$CHO(P)CH_2$), 2.23 (ddd, *J* = 14.5, 11.8, 5.8 Hz, 1H, $H_2C=C(CH_3)CH_2$-$CHO(P)C\underline{H}_aH_bCHO$[P]), 2.09–1.97 (m, 2H, $CH_2(CH_3)C=CHCH_a\underline{H}_bC\underline{H}_aH_bCHO(P)CH_2OBn$), 1.79 (d, *J* = 1.4 Hz, 6H), 1.72 (ddt, *J* = 16.9, 14.7, 2.4 Hz, 3H, $CH_2(P)OCHCH_a\underline{H}_bC(CH_3)=CHCH_2$, $H_2C=C(CH_3)CH_2$-$CHO(P)CH_a\underline{H}_bCHO$[P], $CH_2(CH_3)C=CHCH_2CH_a\underline{H}_bCHO(P)CH_2OBn$);

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ ppm 140.0 (C), 138.3 (C), 131.9 (C), 128.3 (2 x CH), 127.7 (2 x CH), 127.5 (CH), 125.9 (CH), 114.4 ($CH_2$), 75.0 (d, *J* = 7.8 Hz, CH), 74.6 (d, *J* = 5.7 Hz, CH), 74.6 (CH), 73.5 ($CH_2$), 72.0 ($CH_2$), 44.3 (d, *J* = 9.1 Hz, $CH_2$), 35.1 ($CH_2$), 34.5 (d, *J* = 6.8 Hz, $CH_2$), 30.2 (d, *J* = 9.7 Hz, $CH_2$), 22.9 ($CH_3$), 22.7 ($CH_2$), 22.0 ($CH_3$);

**$^{31}$P NMR (162 MHz, $CDCl_3$)** δ ppm –9.52 (d, $J_{PH}$ = 23.3 Hz);

**HRMS (TOF MS ES+)** calcd for $(C_{22}H_{31}O_5P)_2Na$ $(2M+Na)^+$ 835.3716; found 835.3714.

**(4*R*,6*R*)-2-(((*R*)-1-(benzyloxy)hex-5-en-2-yl)oxy)-4,6-bis(2-methylallyl)-1,3,2-dioxaphosphinane 2-oxide** (**2.13.5**):



(*R,R,R*)-**2.13.5**

Following General Procedure 1, monochlorophosphate (*R,R*)-**2.13.2** (0.180 g, 0.680 mmol) and alcohol (*R*)-**2.12.4** (0.129 g, 0.623 mmol) were converted into phosphate triene **2.13.5** (0.201 g, 0.463 mmol, 82%) which was isolated as a pale yellow oil.

**FTIR (neat)**: 2964, 2936, 2860, 1452, 1375, 1366, 1285, 1099, 1070, 999, 899, 810, 737, 698, 548 $cm^{-1}$;

**Optical Rotation** $[\alpha]_D$ = +31.7 (*c* 1.29, $CHCl_3$);

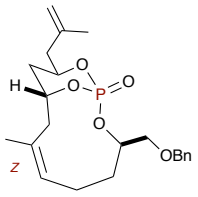
**$^1$H NMR (500 MHz, $CDCl_3$)** δ ppm 7.34 (d, *J* = 4.4 Hz, 4H, aromatic C-H), 7.29 (dd, *J* = 4.9, 3.8 Hz, 1H, aromatic C-H), 5.81 (ddt, *J* = 16.9, 10.2, 6.5 Hz, 1H, $H_2C$=C<u>H</u>-$CH_2$-$CH_2$-CHO(P)$CH_2$OBn), 5.04 (dq, *J* = 17.1, 1.7 Hz, 1H, <u>$H_a$</u>$H_b$C=CH-$CH_2$-$CH_2$-CHO(P)$CH_2$OBn), 4.99 (dd, *J* = 10.2, 1.6 Hz, 1H, $H_a$<u>$H_b$</u>C=CH-$CH_2$-$CH_2$-CHO(P)$CH_2$OBn), 4.85 (dt, *J* = 13.5, 1.7 Hz, 2H, <u>$H_2$</u>C=C($CH_3$)-$CH_2$CHO(P)$CH_2$), 4.79–4.74 (m, 2H, <u>$H_2$</u>C=C($CH_3$)-$CH_2$CHO(P)$CH_2$), 4.74–4.61 (m, 3H, $H_2C$=C($CH_3$)-$CH_2$C<u>H</u>O(P)$CH_2$, $H_2C$=C($CH_3$)-$CH_2$C<u>H</u>O(P)$CH_2$, $H_2C$=CH-$CH_2$-$CH_2$-C<u>H</u>O(P)$CH_2$OBn), 4.59 (d, *J* = 12.0 Hz, 1H, OC<u>$H_a$</u>$H_b$Ph), 4.53 (d, *J* = 12.0 Hz, 1H, OC$H_a$<u>$H_b$</u>Ph), 3.61 (dd, *J* = 4.8, 2.6 Hz, 2H, $H_2C$=CH-$CH_2$-$CH_2$-CHO(P)C<u>$H_2$</u>OBn), 2.57 (td, *J* = 14.5, 6.8 Hz, 2H, $H_2C$=C($CH_3$)-C<u>$H_a$</u>$H_b$CHO(P)$CH_2$, $H_2C$=C($CH_3$)-C<u>$H_a$</u>$H_b$CHO(P)$CH_2$), 2.40–2.30 (m, 2H, $H_2C$=C($CH_3$)-$CH_a$<u>$H_b$</u>CHO(P)$CH_2$, $H_2C$=C($CH_3$)-$CH_a$<u>$H_b$</u>CHO(P)$CH_2$), 2.24–2.08 (m, 2H, $H_2C$=CH-C<u>$H_2$</u>-$CH_2$-CHO(P)$CH_2$OBn), 1.98 (dddd, *J* = 14.3, 8.0, 4.8, 1.4 Hz, 1H, $H_2C$=C($CH_3$)$CH_2$-CHO(P)C<u>$H_a$</u>$H_b$CHO[P],), 1.89 (dddd, *J* = 14.7, 5.7, 4.0, 1.7 Hz, 1H, $H_2C$=C($CH_3$)$CH_2$-CHO(P)$CH_a$<u>$H_b$</u>CHO[P],), 1.82 (dddd, *J* = 8.8, 7.4, 6.2, 1.6 Hz, 2H, $H_2C$=CH-$CH_2$-C<u>$H_2$</u>-CHO(P)$CH_2$OBn), 1.75 (d, *J* = 1.1 Hz, 3H, $H_2C$=C(C<u>$H_3$</u>)-$CH_2$CHO(P)$CH_2$), 1.72 (d, *J* = 1.1 Hz, 3H, $H_2C$=C(C<u>$H_3$</u>)-$CH_2$CHO(P)$CH_2$);

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ ppm 140.4 (C), 140.2 (C), 138.0 (C), 137.4 (CH), 128.3 (2 x CH), 127.59 (2 x CH), 127.57 (CH), 115.2 ($CH_2$), 114.24 ($CH_2$), 114.15 ($CH_2$), 77.7 (d, $J_{CP}$ = 6.3 Hz, CH), 75.6 (d, $J_{CP}$ = 6.7 Hz, CH), 74.6 (d, $J_{CP}$ = 6.5 Hz, CH), 73.2 ($CH_2$), 71.6 (d, $J_{CP}$ = 3.9 Hz, $CH_2$), 43.7 (d, $J_{CP}$ = 7.1 Hz, $CH_2$), 43.0 (d, $J_{CP}$ = 4.1 Hz, $CH_2$), 33.3 (d, $J_{CP}$ = 6.7 Hz, $CH_2$), 31.4 (d, $J_{CP}$ = 5.1 Hz, $CH_2$), 29.2 ($CH_2$), 22.6 ($CH_3$), 22.3 ($CH_3$);

**$^{31}$P NMR (162 MHz, $CDCl_3$)** δ ppm –6.95 (m);

**HRMS (TOF MS ES+)** calcd for $(C_{24}H_{35}O_5P)_2Na$ $(2M+Na)^+$ 891.4342; found 891.4314.

**(1*S*,3*R*,9*R*,11*R*,*Z*)-3-((benzyloxy)methyl)-7-methyl-11-(2-methylallyl)-2,12,13-trioxa-1-phosphabicyclo[7.3.1]tridec-6-ene 1-oxide** (*trans*-**2.13.7**):




*trans*-**2.13.7**

Following General Procedure 2, triene **2.13.5** (30.0 mg, 0.0690 mmol) was exposed to G-II catalyst (2 mol %, over 2 hours) in refluxing $CH_2Cl_2$ to provide the corresponding bicyclic phosphate *trans*-**2.13.7** (24.5 mg, 0.0603 mmol, 87%) as a pale yellow oil. Full characterization in $CDCl_3$ and DMSO-$d_6$ at ambient temperature—even after extended scan times—provided incomplete information for 13C and carbon-related 2D NMR. As such, full characterization of *trans*-**2.13.7** required elevated temperatures (95 °C) to fully identify short, broad carbon signals and correlate these 13C signals to 1H signals (HSQC, HMBC).

**FTIR (neat)**: 2928, 2855, 1450, 1377, 1281, 1103, 1020, 972, 957, 907, 791, 745, 698 $cm^{-1}$;

**Optical Rotation** $[\alpha]_D$ = +57.5 (*c* 0.36, $CHCl_3$);

**$^1$H NMR (500 MHz, 95 °C, DMSO-$d_6$)** δ ppm 7.37–7.26 (m, 5H, aromatic C-H), 5.33 (t, *J* = 8.2 Hz, 1H, $CH_2$(P)OCHC$H_2$C($CH_3$)=C$\underline{H}$C$H_2$), 4.96–4.78 (m, 4H, $\underline{H}_2$C=C($CH_3$)$CH_2$-CHO(P)$CH_2$, $H_2$C=C($CH_3$)$CH_2$-C$\underline{H}$O(P)$CH_2$C$\underline{H}$O[P]), 4.51 (s, 2H, -OC$\underline{H}_2$Ph), 4.24 (q, *J* = 8.8, 5.9 Hz, 1H, $CH_2$($CH_3$)C=CHC$H_2$C$H_2$C$\underline{H}$O(P)$CH_2$OBn), 3.61 (dd, *J* = 10.3, 5.8 Hz, 1H, $CH_2$CHO(P)C$\underline{H}_a$$H_b$OBn), 3.48 (dd, *J* = 10.4, 5.7 Hz, 1H, $CH_2$CHO(P)C$H_a$$\underline{H}_b$OBn), 2.60–2.52 (s, 1H, $CH_2$(P)OCHC$\underline{H}_a$$H_b$C($CH_3$)=C$H_2$), 2.49–2.34 (m, 4H,

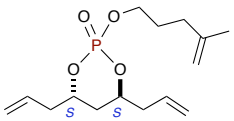
$CH_2(P)OCHCH_a\underline{H}_bC(CH_3)=CHCH_2$, $CH_2(CH_3)C=CHC\underline{H}_aH_bCH_2CHO(P)CH_2OBn$, $H_2C=C(CH_3)C\underline{H}_2$-CHO(P)$CH_2$), 2.18 (s, 1H, $CH_2(CH_3)C=CHCH_a\underline{H}_bCH_2CHO(P)CH_2OBn$), 1.99 (q, $J$ = 5.9, 5.1 Hz, 2H, $H_2C=C(CH_3)CH_2$-CHO(P)$C\underline{H}_2CHO$[P]), 1.75 (m, $J$ = 6.8 Hz, 7H, $CH_2(CH_3)C=CHCH_2C\underline{H}_aH_bCHO(P)CH_2OBn$, $CH_2(P)OCHCH_2C(C\underline{H}_3)=CHCH_2$, $H_2C=C(C\underline{H}_3)CH_2$-CHO(P)$CH_2$), 1.63 (tt, $J$ = 10.2, 5.1 Hz, 1H, $CH_2(CH_3)C=CHCH_2CH_a\underline{H}_bCHO(P)CH_2OBn$);

**$^{13}$C NMR (126 MHz, 95 °C, DMSO-$d_6$)** δ ppm 140.3 (C), 138.0 (C), 130.7 (C), 128.3 (CH), 127.8 (2 x CH), 127.03 (2 x CH), 126.95 (CH), 113.2 ($CH_2$), 76.6 (s, br, CH), 76.0 (d, $J_{CP}$ = 6.7 Hz, CH), 75.5 (d, $J_{CP}$ = 8.3 Hz, CH), 72.01 ($CH_2$), 71.98 ($CH_2$), 42.3 (d, $J_{CP}$ = 4.5 Hz, $CH_2$), 35.8 ($CH_2$), 32.0 (s, br, $CH_2$), 30.7 (d, $J_{CP}$ = 3.7 Hz, $CH_2$), 24.9 (s, br, $CH_3$), 23.9 ($CH_2$), 21.9 ($CH_3$);

**$^{31}$P NMR (162 MHz, 95 °C, DMSO-$d_6$)** δ ppm –14.7 (s);

**HRMS (TOF MS ES+)** calcd for $(C_{22}H_{31}O_5P)_2Na$ $(2M+Na)^+$ 835.3716; found 835.3685.

**(4*S*,6*S*)-4,6-diallyl-2-((4-methylpent-4-en-1-yl)oxy)-1,3,2-dioxaphosphinane 2-oxide (2.14.1)**:




(*S,S*)-**2.14.1**

Following General Procedure 1, monochlorophosphate (*S,S*)-**2.12.3** (0.2593 g, 1.096 mmol) and 4-methyl-4-penten-1-ol (0.1006 g, 1.005 mmol) were converted into **2.14.1** (0.2456 g, 0.8178 mmol, 90%) which was isolated as a colorless oil.

**FTIR (neat)**: 2959, 2937, 1443, 1373, 1286, 1096, 1078, 1015, 974, 918, 898, 814, 631, 509 $cm^{-1}$;

**Optical Rotation** $[\alpha]_D = -35.2$ (*c* 0.84, $CHCl_3$);

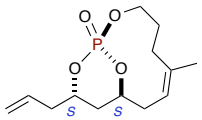
**$^1$H NMR (500 MHz, $CDCl_3$)** δ ppm 5.84–5.72 (m, 2H, $H_2C$=C<u>H</u>-$CH_2CHO(P)CH_2$, $H_2C$=C<u>H</u>-$CH_2CHO(P)CH_2$), 5.18–5.12 (m, 4H, <u>$H_2$</u>C=CH-$CH_2CHO(P)CH_2$, <u>$H_2$</u>C=CH-$CH_2CHO(P)CH_2$), 4.76–4.73 (m, 1H, <u>$H_a$</u>$H_b$C=C($CH_3$)-$CH_2$-$CH_2$-$CH_2O(P)$), 4.69 (dt, *J* = 2.3, 1.1 Hz, 1H, $H_a$<u>$H_b$</u>C=C($CH_3$)-$CH_2$-$CH_2$-$CH_2O(P)$), 4.61 (dddd, *J* = 14.4, 12.0, 7.0, 5.0 Hz, 1H, $H_2C$=CH$CH_2$-C<u>H</u>O(P)$CH_2$), 4.54–4.46 (m, 1H, $H_2C$=CH$CH_2$-C<u>H</u>O(P)$CH_2$), 4.09 (dt, *J* = 8.1, 6.6 Hz, 2H, $H_2C$=C($CH_3$)-$CH_2$-$CH_2$-C<u>$H_2$</u>O(P)), 2.66 (ddd, *J* = 7.0, 13.9, 7.0 Hz, 1H, $H_2C$=CHC<u>$H_a$</u>$H_b$-CHO(P)$CH_2$), 2.56 (ddd, *J* = 7.0, 13.9, 7.0 Hz, 1H, $H_2C$=CHC<u>$H_a$</u>$H_b$-CHO(P)$CH_2$), 2.39 (ddd, *J* = 7.0, 14.1, 7.0 Hz 2H, $H_2C$=CHC$H_a$<u>$H_b$</u>-CHO(P)$CH_2$, $H_2C$=CHC$H_a$<u>$H_b$</u>-CHO(P)$CH_2$), 2.09 (dd, *J* = 7.33, 7.33 Hz, 2H, $H_2C$=C($CH_3$)-C<u>$H_2$</u>-$CH_2$-$CH_2O(P)$), 2.02 (dddd, *J* = 14.9, 8.6, 5.0, 1.4 Hz, 1H, $H_2C$=CH$CH_2$-CHO(P)C<u>$H_a$</u>$H_b$CHO[P]), 1.90–1.80 (m, 3H, $H_2C$=CH$CH_2$-CHO(P)C$H_a$<u>$H_b$</u>CHO[P], $H_2C$=C($CH_3$)-$CH_2$-C<u>$H_2$</u>-$CH_2O(P)$), 1.74–1.69 (m, 3H, $H_2C$=C(C<u>$H_3$</u>)-$CH_2$-$CH_2$-$CH_2O(P)$);

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ ppm 144.4 (C), 132.6 (CH), 132.2 (CH), 119.0 ($CH_2$), 118.8 ($CH_2$), 110.6 ($CH_2$), 77.0 (d, $J_{CP}$ = 6.8 Hz, CH), 75.5 (d, $J_{CP}$ = 6.6 Hz, CH), 67.5 (d, $J_{CP}$ = 5.9 Hz, $CH_2$), 40.0 (d, $J_{CP}$ = 7.4 Hz, $CH_2$), 38.9 (d, $J_{CP}$ = 3.2 Hz, $CH_2$), 33.6 ($CH_2$), 33.1 (d, $J_{CP}$ = 6.8 Hz, $CH_2$), 28.3 (d, $J_{CP}$ = 6.6 Hz, $CH_2$), 22.4 ($CH_3$);

**$^{31}$P NMR (162 MHz, $CDCl_3$)** δ ppm –6.77 (dd, $J_{PH}$ = 14.3, 7.0 Hz);

**HRMS (TOF MS ES+)** calcd for $(C_{15}H_{25}O_4P)_2Na$ $(2M+Na)^+$ 623.2879; found 623.2886.

**(1*R*,9*S*,11*S*,*Z*)-11-allyl-6-methyl-2,12,13-trioxa-1-phosphabicyclo[7.3.1]tridec-6-ene 1-oxide** (**2.14.3**):



**2.14.3**

To a clean, dry, round bottom flask, equipped with a stirbar, was added triene **2.14.1** (25.0 mg, 0.0832 mmol), toluene (dry, degassed, 84 mL), and Ru-**2.14.2** catalyst (3.3 mg, 0.00416 mmol, 5 mol %). High vacuum was applied to the flask (1 min), and the flask was charged with Ar (repeated 5 times). The flask was equipped with an Ar inlet and heated to 35 °C. The reaction stirred at 35 °C for 2.5 hours, where another 5 mol % of Ru-**2.14.2** (3.3 mg, 0.00416 mmol) was added. The reaction continued to stir for 1 hour (monitored by TLC), at which point 5 drops of DMSO were added, and the solvent was removed under reduced pressure. The crude mixture was separated by flash chromatography (silica, 0%-50% EtOAc in hexanes) to provide **2.14.3** (5.8 mg, 0.0213 mmol, 26%) as a colorless oil.

**FTIR (neat)**: 2961, 2928, 1464, 1433, 1281, 1223, 1105, 1072, 1013, 978, 912, 866, 804, 552 $cm^{-1}$;

**Optical Rotation** $[\alpha]_D = -33.5$ (*c* 0.19, $CHCl_3$);

**$^1$H NMR (500 MHz, $CDCl_3$)** δ ppm 5.89–5.78 (m, 1H, $CH_2(P)OCHCH_2C\underline{H}=CH_2$), 5.37 (dd, *J* = 11.5, 2.4 Hz, 1H, $CH_2(P)OCHCH_2C\underline{H}=C(CH_3)CH_2$), 5.20–5.17 (m, 1H, $CH_2(P)OCHCH_2CH=C\underline{H_a}H_b$), 5.16 (t, *J* = 1.3 Hz, 1H, $CH_2(P)OCHCH_2CH=CH_a\underline{H_b}$), 4.78 (dtd, *J* = 12.2, 6.2, 2.0 Hz, 1H, $CH_2(P)OC\underline{H}CH_2CH=CH_2$), 4.70–4.59 (m, 1H, $CH_2(P)OC\underline{H}CH_2CH=C(CH_3)CH_2$), 4.06 (ddd, *J* = 9.9, 4.6, 1.6 Hz, 1H, $(P)OC\underline{H_a}H_bCH_2CH_2C(CH_3)=CHCH_2$), 3.92 (dddd, *J* = 12.8, 9.9, 5.9, 2.6 Hz, 1H,

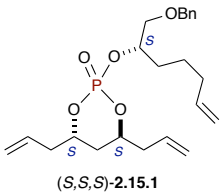
(P)OCH$_a$$\underline{H}_b$CH$_2$CH$_2$C(CH$_3$)=CHCH$_2$), 3.16 (dt, $J$ = 14.3, 12.5 Hz, 1H, CH$_2$(P)OCHC$\underline{H}_a$H$_b$CH=C(CH$_3$)CH$_2$), 2.72 (td, $J$ = 13.1, 5.3 Hz, 1H, (P)OCH$_2$CH$_2$C$\underline{H}_a$H$_b$C(CH$_3$)=CHCH$_2$), 2.57–2.46 (m, 1H, CH$_2$(P)OCHC$\underline{H}_a$H$_b$CH=CH$_2$), 2.44–2.33 (m, 1H, CH$_2$(P)OCHCH$_a$$\underline{H}_b$CH=CH$_2$), 2.22 (dddd, $J$ = 14.6, 12.0, 5.5, 0.8 Hz, 1H, H$_2$C=CHCH$_2$-CHO(P)C$\underline{H}_a$H$_b$CHO[P]), 1.95 (dddt, $J$ = 15.0, 10.1, 5.1, 2.7 Hz, 2H, CH$_2$(P)OCHCH$_a$$\underline{H}_b$CH=C(CH$_3$)CH$_2$, (P)OCH$_2$C$\underline{H}_a$H$_b$CH$_2$C(CH$_3$)=CHCH$_2$), 1.89–1.81 (m, 1H, (P)OCH$_2$CH$_2$CH$_a$$\underline{H}_b$C(CH$_3$)=CHCH$_2$), 1.78–1.72 (m, 1H, (P)OCH$_2$CH$_a$$\underline{H}_b$CH$_2$C(CH$_3$)=CHCH$_2$), 1.71 (dd, $J$ = 1.7, 1.7 Hz, 3H, CH$_2$(P)OCHCH$_2$CH=C(C$\underline{H}_3$)CH$_2$), 1.70–1.66 (m, 1H, H$_2$C=CHCH$_2$-CHO(P)CH$_a$$\underline{H}_b$CHO[P]);

**$^{13}$C NMR (126 MHz, CDCl$_3$)** δ ppm 135.2 (C), 132.0 (CH), 122.2 (CH$_2$), 119.0 (CH$_2$), 77.5 (d, $J_{CP}$ = 7.3 Hz, CH), 75.9 (d, $J_{CP}$ = 7.3 Hz, CH), 63.9 (d, $J_{CP}$ = 4.9 Hz, CH$_2$), 40.6 (d, $J_{CP}$ = 9.0 Hz, CH$_2$), 34.5 (d, $J_{CP}$ = 6.7 Hz, CH$_2$), 32.6 (CH$_2$), 26.1 (CH$_2$), 24.9 (d, $J_{CP}$ = 10.0 Hz, CH$_2$), 22.5 (CH$_3$);

**$^{31}$P NMR (162 MHz, CDCl$_3$)** δ ppm –8.22 (d, $J_{PH}$ = 24.1 Hz);

**HRMS (TOF MS ES+)** calcd for (C$_{13}$H$_{21}$O$_4$P)$_2$Na (2M+Na)$^+$ 567.2253; found 567.2241.

**(4*S*,6*S*)-4,6-diallyl-2-(((*S*)-1-(benzyloxy)hept-6-en-2-yl)oxy)-1,3,2-dioxaphosphinane 2-oxide** (**2.15.1**):




(*S,S,S*)-**2.15.1**

Following General Procedure 1, monochlorophosphate (*S,S*)-**2.12.3** (0.117 g, 0.494 mmol) and alcohol (*S*)-**2.15.3**[5] (0.0990 g, 0.450 mmol) were converted into **2.15.1** (0.109 g, 0.259 mmol, 58%) which was isolated as a pale yellow oil.

**FTIR (neat)**: 2932, 2862, 1454, 1435, 1362, 1286, 1097, 1007, 976, 916, 797, 739, 698, 629, 513 $cm^{-1}$;

**Optical Rotation** $[\alpha]_D = -33.2$ (*c* 1.13, $CHCl_3$);

**$^1$H NMR (500 MHz, $CDCl_3$)** δ ppm 7.34 (d, *J* = 4.4 Hz, 4H, aromatic C-H), 7.32–7.27 (m, 1H, aromatic C-H), 5.85–5.68 (m, 3H, $H_2C$=C<u>H</u>-$CH_2CHO(P)CH_2$, $H_2C$=C<u>H</u>-$CH_2CHO(P)CH_2$, $H_2C$=C<u>H</u>-$CH_2$-$CH_2$-$CH_2$-$CHO(P)CH_2OBn$), 5.16 (dt, *J* = 9.0, 1.5 Hz, 1H, <u>$H_a$</u>$H_b$C=CH-$CH_2CHO(P)CH_2$), 5.13 (dt, *J* = 3.6, 1.3 Hz, 2H, $H_a$<u>$H_b$</u>C=CH-$CH_2CHO(P)CH_2$, <u>$H_a$</u>$H_b$C=CH-$CH_2CHO(P)CH_2$), 5.10 (q, *J* = 1.6 Hz, 1H, $H_a$<u>$H_b$</u>C=CH-$CH_2CHO(P)CH_2$), 5.04–4.99 (m, 1H, <u>$H_a$</u>$H_b$C=CH-$CH_2$-$CH_2$-$CH_2$-$CHO(P)CH_2OBn$), 4.97 (ddd, *J* = 10.2, 2.2, 1.1 Hz, 1H, $H_a$<u>$H_b$</u>C=CH-$CH_2$-$CH_2$-$CH_2$-$CHO(P)CH_2OBn$), 4.65–4.48 (m, 5H, $H_2C$=CH$CH_2$-C<u>H</u>O(P)$CH_2$, $H_2C$=CH$CH_2$-C<u>H</u>O(P)$CH_2$, C<u>H</u>O(P)$CH_2OBn$, OC<u>$H_2$</u>Ph), 3.61 (dd, *J* = 4.9, 3.5 Hz, 2H, $H_2C$=CH-$CH_2$-$CH_2$-$CH_2$-CHO(P)C<u>$H_2$</u>OBn), 2.63 (ddd, *J* = 6.7, 13.9, 6.7 Hz, 1H, $H_2C$=CH-C<u>$H_a$</u>$H_b$CHO(P)$CH_2$), 2.56 (m, ddd, *J* = 6.3, 13.5, 6.3 Hz, 1H, $H_2C$=CH-C<u>$H_a$</u>$H_b$CHO(P)$CH_2$), 2.43–2.33 (m, 2H, $H_2C$=CH-$CH_a$<u>$H_b$</u>CHO(P)$CH_2$, $H_2C$=CH-$CH_a$<u>$H_b$</u>CHO(P)$CH_2$), 2.09 (dtdd, *J* = 7.9, 6.6, 4.1, 1.3 Hz,

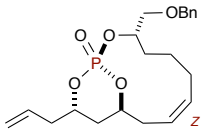
2H, $H_2C$=CH-C<u>$H_2$</u>-$CH_2$-$CH_2$-CHO(P)$CH_2$OBn), 2.00 (dddd, *J* = 14.6, 8.4, 5.0, 1.3 Hz, 1H, $H_2C$=CH$CH_2$-CHO(P)C<u>$H_a$</u>$H_b$CHO[P]), 1.89 (dddd, *J* = 14.6, 5.7, 4.0, 1.7 Hz, 1H, $H_2C$=CH$CH_2$-CHO(P)$CH_a$<u>$H_b$</u>CHO[P]), 1.73 (dt, *J* = 8.6, 6.8 Hz, 2H, $H_2C$=CH-$CH_2$-$CH_2$-C<u>$H_2$</u>-CHO(P)$CH_2$OBn), 1.57–1.42 (m, 2H, $H_2C$=CH-$CH_2$-C<u>$H_2$</u>-$CH_2$-CHO(P)$CH_2$OBn);

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ ppm 138.2 (CH), 138.0 (C), 132.6 (CH), 132.3 (CH), 128.3 (CH), 127.62 (2 x CH), 127.59 (2 x CH), 118.8 ($CH_2$), 118.7 ($CH_2$), 114.9 ($CH_2$), 78.2 (d, $J_{CP}$ = 6.3 Hz, CH), 76.8 (d, $J_{CP}$ = 6.9 Hz, CH), 75.4 (d, $J_{CP}$ = 6.8 Hz, CH), 73.2 ($CH_2$), 71.7 (d, $J_{CP}$ = 4.1 Hz, $CH_2$), 40.0 (d, $J_{CP}$ = 7.3 Hz, $CH_2$), 39.1 (d, $J_{CP}$ = 4.0 Hz, $CH_2$), 33.4 ($CH_2$), 33.1 (d, $J_{CP}$ = 6.7 Hz, $CH_2$), 31.6 (d, $J_{CP}$ = 4.9 Hz, $CH_2$), 24.3 ($CH_2$);

**$^{31}$P NMR (162 MHz, $CDCl_3$)** δ ppm –6.96 (dt, $J_{PH}$ = 13.6, 7.0 Hz);

**HRMS (TOF MS ES+)** calcd for $(C_{23}H_{33}O_5P)_2Na$ $(2M+Na)^+$ 863.4029; found 863.4056.

**(1*R*,3*S*,10*S*,12*S*,*Z*)-12-allyl-3-((benzyloxy)methyl)-2,13,14-trioxa-1-phosphabicyclo[8.3.1]tetradec-7-ene 1-oxide** (*trans*-**2.15.4**):



*trans*-**2.15.4**

Following General Procedure 2, triene **2.15.1** (20.0 mg, 0.0476 mmol) was exposed to G-I catalyst (2 mol %, over 3 hours) in refluxing $CH_2Cl_2$ to provide the corresponding bicyclic phosphate *trans*-**2.15.4** (11.8 mg, 0.0301 mmol, 63%) as a colorless oil.

**FTIR (neat)**: 2922, 2860, 1452, 1364, 1273, 1097, 1012, 972, 953, 920, 791, 735, 698, 554 $cm^{-1}$;

**Optical Rotation** $[\alpha]_D$ = –63.9 (*c* 0.44, $CHCl_3$);

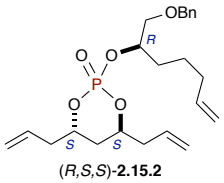
**$^{1}$H NMR (500 MHz, $CDCl_3$)** δ ppm 7.39–7.32 (m, 4H, Aromatic C-H), 7.32–7.27 (m, 1H, Aromatic C-H), 5.80 (dddd, *J* = 16.9, 10.2, 7.5, 6.5 Hz, 1H, $CH_2$(P)OCHCH$_2$C<u>H</u>=CH$_2$), 5.58–5.47 (m, 2H, $CH_2$(P)OCHCH$_2$C<u>H</u>=C<u>H</u>CH$_2$), 5.16 (dq, *J* = 17.2, 1.6 Hz, 1H, $CH_2$(P)OCHCH$_2$CH=C<u>H$_a$</u>H$_b$), 5.12 (ddt, *J* = 10.2, 2.1, 1.2 Hz, 1H, $CH_2$(P)OCHCH$_2$CH=CH$_a$<u>H$_b$</u>), 4.72–4.61 (m, 3H, $CH_2$(P)OC<u>H</u>CH$_2$CH=CHCH$_2$, $CH_2$(P)OC<u>H</u>CH$_2$CH=CH$_2$, –OC<u>H$_a$</u>H$_b$Ph), 4.57 (d, *J* = 11.8 Hz, 1H, –OCH$_a$<u>H$_b$</u>Ph), 4.38–4.27 (m, 1H, -CH$_2$HC=CHCH$_2$CH$_2$CH$_2$C<u>H</u>O(P)CH$_2$OBn), 3.72–3.55 (m, 2H, CH$_2$CHO(P)C<u>H$_2$</u>OBn), 2.98–2.89 (m, 1H, $CH_2$(P)OCHC<u>H$_a$</u>H$_b$CH=CHCH$_2$), 2.62–2.45 (m, 2H, $CH_2$(P)OCHC<u>H$_a$</u>H$_b$CH=CH$_2$, H$_2$C=CHCH$_2$-CHO(P)C<u>H$_a$</u>H$_b$CHO[P]), 2.45–2.34 (m, 2H, $CH_2$(P)OCHCH$_a$<u>H$_b$</u>CH=CH$_2$, CH$_2$HC=CHC<u>H$_a$</u>H$_b$CH$_2$CH$_2$CHO(P)), 2.00–1.86 (m, 3H, $CH_2$(P)OCHCH$_a$<u>H$_b$</u>CH=CHCH$_2$, CH$_2$HC=CHCH$_2$C<u>H$_a$</u>H$_b$CH$_2$CHO(P), CH$_2$HC=CHCH$_a$<u>H$_b$</u>CH$_2$CH$_2$CHO(P)), 1.83 (dtd, *J* = 15.1, 2.8, 1.5 Hz, 1H, H$_2$C=CHCH$_2$-CHO(P)CH$_a$<u>H$_b$</u>CHO[P]), 1.62–1.57 (m, 1H, CH$_2$HC=CHCH$_2$CH$_a$<u>H$_b$</u>CH$_2$CHO(P)), 1.53 (dqd, *J* = 10.7, 5.3, 3.6 Hz, 2H, CH$_2$HC=CHCH$_2$CH$_2$C<u>H$_2$</u>CHO(P));

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ ppm 138.1 (C), 132.8 (CH), 132.1 (CH), 128.3 (2 x CH), 127.7 (2 x CH), 127.6 (CH), 125.1 (CH), 118.9 ($CH_2$), 77.5 (d, $J_{CP}$ = 8.4 Hz, CH), 76.9 (d, $J_{CP}$ = 6.5 Hz, CH), 76.4 (d, $J_{CP}$ = 6.1 Hz, CH), 73.6 ($CH_2$), 72.3 (d, $J_{CP}$ = 6.8 Hz, $CH_2$), 40.9 (d, $J_{CP}$ = 4.6 Hz, $CH_2$), 34.5 (d, $J_{CP}$ = 12.0 Hz, $CH_2$), 33.1 (d, $J_{CP}$ = 3.1 Hz, $CH_2$), 28.9 ($CH_2$), 24.1 ($CH_2$), 23.8 ($CH_2$);

**$^{31}$P NMR (162 MHz, $CDCl_3$)** δ ppm –10.13 (m);

**HRMS (TOF MS ES+)** calcd for $(C_{21}H_{29}O_5P)_2Na$ $(2M+Na)^+$ 807.3403; found 807.3404.

**(4*S*,6*S*)-4,6-diallyl-2-(((*R*)-1-(benzyloxy)hept-6-en-2-yl)oxy)-1,3,2-dioxaphosphinane 2-oxide** (**2.15.2**):



(*R*,*S*,*S*)-**2.15.2**

Following General Procedure 1, monochlorophosphate (*S,S*)-**2.12.3** (0.117 g, 0.494 mmol) and alcohol (*R*)-**2.15.3**[12] (0.0990 g, 0.450 mmol) were converted into **2.15.2** (0.120 g, 0.259 mmol, 63%) which was isolated as a colorless oil.

**FTIR (neat)**: 2930, 2862, 1454, 1435, 1362, 1288, 1099, 1078, 999, 974, 916, 800, 739, 698, 629, 548 $cm^{-1}$;

**Optical Rotation** $[\alpha]_D = -39.7$ (*c* 1.08, $CHCl_3$);

**$^1$H NMR (500 MHz, $CDCl_3$)** δ ppm 7.36–7.28 (m, 5H, aromatic C-H), 5.83–5.73 (m, 2H, $H_2C$=C<u>H</u>-$CH_2CHO(P)CH_2$, $H_2C$=C<u>H</u>-$CH_2CHO(P)CH_2$), 5.73–5.63 (m, 1H, $H_2C$=C<u>H</u>-$CH_2$-$CH_2$-$CH_2$-$CHO(P)CH_2OBn$), 5.14–5.10 (m, 2H, <u>H</u>$_a$H$_b$C=CH-$CH_2CHO(P)CH_2$, <u>H</u>$_a$H$_b$C=CH-$CH_2CHO(P)CH_2$), 5.10–5.07 (m, 2H, H$_a$<u>H</u>$_b$C=CH-$CH_2CHO(P)CH_2$, H$_a$<u>H</u>$_b$C=CH-$CH_2CHO(P)CH_2$), 5.01 (dq, *J* = 17.1, 1.7 Hz, 1H, <u>H</u>$_a$H$_b$C=CH-$CH_2$-$CH_2$-$CH_2$-$CHO(P)CH_2OBn$), 4.95 (ddt, *J* = 10.2, 2.3, 1.2 Hz, 1H, H$_a$<u>H</u>$_b$C=CH-$CH_2$-$CH_2$-$CH_2$-$CHO(P)CH_2OBn$), 4.61–4.50 (m, 5H, $H_2C$=$CHCH_2$-C<u>H</u>$O(P)CH_2$, $H_2C$=$CHCH_2$-C<u>H</u>$O(P)CH_2$, C<u>H</u>$O(P)CH_2OBn$, OC<u>H</u>$_2$Ph), 3.62–3.54 (m, 2H, $H_2C$=CH-$CH_2$-$CH_2$-$CH_2$-$CHO(P)C$<u>H</u>$_2OBn$), 2.72–2.64 (m, 1H, $H_2C$=CH-C<u>H</u>$_a$H$_b$$CHO(P)CH_2$), 2.48–2.41 (m, 1H, $H_2C$=CH-C<u>H</u>$_a$H$_b$$CHO(P)CH_2$), 2.41–2.34 (m,

[12] Ichimoto, I.; Ohotomo, Y.; Kirihata, M.; Tsuji, H.; Ueda, H. Stereoselective Synthesis of (–)-Patulolide B, a New Macrolide from a Strain of *Penicillium urticae*. *Chemistry Express* **1989**, *4*, 625–628.

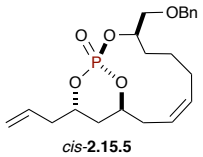
1H, $H_2C$=CH-$CH_a\underline{H}_bCHO(P)CH_2$), 2.34–2.25 (m, 1H, $H_2C$=CH-$CH_a\underline{H}_bCHO(P)CH_2$), 2.12–2.04 (m, 2H, $H_2C$=CH-$C\underline{H}_2$-$CH_2$-$CH_2$-CHO(P)$CH_2$OBn), 1.96 (dddd, $J$ = 14.8, 8.7, 5.0, 1.4 Hz, 1H, $H_2C$=$CHCH_2$-CHO(P)$C\underline{H}_aH_b$CHO[P]), 1.82 (dddd, $J$ = 14.6, 5.1, 3.7, 1.8 Hz, 1H, $H_2C$=$CHCH_2$-CHO(P)$CH_a\underline{H}_b$CHO[P]), 1.78–1.66 (m, 2H, $H_2C$=CH-$CH_2$-$CH_2$-$C\underline{H}_2$-CHO(P)$CH_2$OBn), 1.58–1.41 (m, 2H, $H_2C$=CH-$CH_2$-$C\underline{H}_2$-$CH_2$-CHO(P)$CH_2$OBn);

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ ppm 138.3 (CH), 137.9 (C), 132.8 (CH), 132.3 (CH), 128.3 (2 x CH), 127.7 (CH), 127.6 (2 x CH), 118.7 ($CH_2$), 118.6 ($CH_2$), 114.8 ($CH_2$), 77.8 (d, $J_{CP}$ = 6.2 Hz, CH), 77.4 (d, $J_{CP}$ = 6.9 Hz, CH), 74.9 (d, $J_{CP}$ = 6.5 Hz, CH), 73.2 ($CH_2$), 71.9 (d, $J_{CP}$ = 4.5 Hz, $CH_2$), 40.0 (d, $J_{CP}$ = 7.8 Hz, $CH_2$), 38.8 (d, $J_{CP}$ = 3.2 Hz, $CH_2$), 33.4 ($CH_2$), 33.0 (d, $J_{CP}$ = 6.7 Hz, $CH_2$), 31.7 (d, $J_{CP}$ = 4.5 Hz, $CH_2$), 24.2 ($CH_2$);

**$^{31}$P NMR (162 MHz, $CDCl_3$)** δ ppm –7.15 (dt, $J_{PH}$ = 13.0, 5.4 Hz);

**HRMS (TOF MS ES+)** calcd for $(C_{23}H_{33}O_5P)_2Na$ $(2M+Na)^+$ 863.4029; found 863.4053.

**(1*R*,3*R*,10*S*,12*S*,*Z*)-12-allyl-3-((benzyloxy)methyl)-2,13,14-trioxa-1-phosphabicyclo[8.3.1]tetradec-7-ene 1-oxide** (*cis*-**2.15.5**, *Z*-product [major]):




*cis*-**2.15.5**

Following General Procedure 2, triene **2.15.2** (25.0 mg, 0.0595 mmol) was exposed to G-I catalyst (3 mol %, over 4 hours) in refluxing $CH_2Cl_2$ to provide the corresponding bicyclic phosphates *cis*-**2.15.5** (13.8 mg, 0.0352 mmol, 59% combined yield, colorless oil) as 2:1 mixture of *Z*/*E*-isomers, which was further purified to a 10:1 mixture of Z/E-isomers for full characterization of the major product.

**FTIR (neat)**: 2930, 2862, 1452, 1362, 1283, 1101, 1078, 1042, 997, 974, 918, 826, 795, 739, 698, 557 $cm^{-1}$;

**Optical Rotation** $[\alpha]_D = -41.0$ (*c* 0.20, $CHCl_3$);

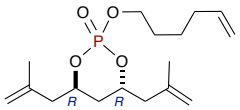
**$^1$H NMR (500 MHz, $CDCl_3$)** δ ppm 7.38–7.33 (m, 4H, Aromatic C-H), 7.32–7.28 (m, 1H, Aromatic C-H), 5.79 (dddd, *J* = 17.0, 10.2, 7.5, 6.5 Hz, 1H, $CH_2(P)OCHCH_2C\underline{H}=CH_2$), 5.49 (dddd, *J* = 10.8, 10.8, 3.3, 2.0 Hz, 1H, $CH_2(P)OCHCH_2C\underline{H}=CHCH_2$), 5.47 (dddd, *J* = 11.0, 11.0, 3.2, 1.9 Hz, 1H, $CH_2(P)OCHCH_2CH=C\underline{H}CH_2$), 5.14 (dq, *J* = 17.1, 1.6 Hz, 1H, $CH_2(P)OCHCH_2CH=C\underline{H}_aH_b$), 5.10 (ddd, *J* = 10.2, 2.0, 1.0 Hz, 1H, $CH_2(P)OCHCH_2CH=CH_a\underline{H}_b$), 5.06 (dtd, *J* = 9.9, 4.8, 2.5 Hz, 1H, $CH_2C\underline{H}O(P)CH_2OBn$), 4.72–4.65 (m, 1H, $CH_2(P)OC\underline{H}CH_2CH=CH_2$), 4.61 (m, 2H, $CH_2(P)OC\underline{H}CH_2CH=CHCH_2$, $-OC\underline{H}_aH_bPh$), 4.56 (d, *J* = 12.3 Hz, 1H, $-OCH_a\underline{H}_bPh$), 3.70–3.65 (m, 1H, $CH_2CHO(P)C\underline{H}_aH_bOBn$), 3.58 (ddd, *J* = 10.5, 5.3, 2.0 Hz, 1H, $CH_2CHO(P)CH_a\underline{H}_bOBn$), 3.19 (ddd, *J* = 14.5, 12.6, 10.5 Hz, 1H, $CH_2(P)OCHC\underline{H}_aH_bCH=CHCH_2$), 2.63–2.53 (m, 1H, $-CH_2HC=CHC\underline{H}_aH_bCH_2CH_2CHO(P)$), 2.48 (dddd, *J* = 12.8, 7.8, 4.9, 1.4 Hz, 1H, $CH_2(P)OCHC\underline{H}_aH_bCH=CH_2$), 2.40–2.32 (m, 1H, $CH_2(P)OCHCH_a\underline{H}_bCH=CH_2$), 2.25–2.16 (m, 1H, $H_2C=CHCH_2$-$CHO(P)C\underline{H}_aH_bCHO[P]$), 1.95 (ddt, *J* = 15.6, 12.9, 2.9 Hz, 2H, $-CH_2HC=CHCH_a\underline{H}_bCH_2C\underline{H}_aH_bCHO(P)$), 1.87 (dt, *J* = 14.8, 2.7 Hz, 1H, $CH_2(P)OCHCH_a\underline{H}_bCH=CHCH_2$), 1.78 (tdd, *J* = 16.0, 6.1, 3.5 Hz, 1H, $-CH_2HC=CHCH_2C\underline{H}_aH_bCH_2CHO(P)$), 1.73–1.65 (m, 2H, $CH_2HC=CHCH_2CH_2CH_a\underline{H}_bCHO(P)$, $H_2C=CHCH_2$-$CHO(P)CH_a\underline{H}_bCHO[P]$), 1.45 (ddtd, *J* = 14.6, 12.2, 4.8, 2.8 Hz, 1H, $-CH_2HC=CHCH_2CH_a\underline{H}_bCH_2CHO(P)$);

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ ppm 138.1 (C), 132.5 (CH), 132.1 (CH), 128.3 (2 x CH), 127.6 (CH), 127.5 (2 x CH), 125.3 (CH), 118.8 ($CH_2$), 78.1 (d, $J_{CP}$ = 7.8 Hz, CH), 77.9 (d, $J_{CP}$ = 6.8 Hz, CH), 75.0 (d, $J_{CP}$ = 7.2 Hz, CH), 72.9 ($CH_2$), 70.3 (d, $J_{CP}$ = 6.6 Hz, $CH_2$), 40.6 (d, $J_{CP}$ = 9.0 Hz, $CH_2$), 34.4 (d, $J_{CP}$ = 6.7 Hz, $CH_2$), 32.4 ($CH_2$), 28.4 (d, $J_{CP}$ = 2.2 Hz, $CH_2$), 25.8 ($CH_2$), 22.9 ($CH_2$);

**$^{31}$P NMR (162 MHz, $CDCl_3$)** δ ppm –8.85 (dd, $J_{PH}$ = 23.8, 9.5 Hz);

**HRMS (TOF MS ES+)** calcd for $(C_{21}H_{29}O_5P)_2Na$ $(2M+Na)^+$ 807.3403; found 807.3422.

**(4*R*,6*R*)-2-(hex-5-en-1-yloxy)-4,6-bis(2-methylallyl)-1,3,2-dioxaphosphinane 2-oxide (2.16.1)**:



(*R,R*)-**2.16.1**

Following General Procedure 1, (*R,R*)-monochlorophosphate **2.13.2** (0.215 g, 0.812 mmol) and 5-hexen-1-ol (74.6 mg, 0.745 mmol) were converted to phosphate triene **2.16.1** (0.193 g, 0.5877 mmol, 87%) which was isolated as a colorless oil.

**FTIR (neat)**: 2964, 2936, 2858, 1443, 1377, 1288, 1026, 1007, 970, 893, 799, 546 $cm^{-1}$;

**Optical Rotation** $[\alpha]_D$ = +44.3 (*c* 0.14, $CHCl_3$);

**$^1$H NMR (500 MHz, $CDCl_3$)** δ ppm 5.79 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H, (P)$OCH_2CH_2CH_2CH_2C\underline{H}=CH_2$), 5.02 (dd, *J* = 17.2, 1.9 Hz, 1H, (P)$OCH_2CH_2CH_2CH=C\underline{H}_aH_b$), 4.97 (dd, *J* = 10.3, 1.7 Hz, 1H, (P)$OCH_2CH_2CH_2CH=CH_a\underline{H}_b$), 4.87 (q, *J* = 1.7 Hz, 2H, (P)$OCH_2CH_2CH_2C(CH_3)=C\underline{H}_aH_b$, (P)$OCH_2CH_2CH_2C(CH_3)=C\underline{H}_aH_b$), 4.79–4.77 (m, 2H, (P)$OCH_2CH_2CH_2C(CH_3)=CH_a\underline{H}_b$, (P)$OCH_2CH_2CH_2C(CH_3)=CH_a\underline{H}_b$), 4.78 (d, *J* = 7.0 Hz,

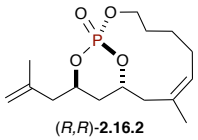
1H, $H_2C$=C($CH_3$)-$CH_2C\underline{H}O$(P)$CH_2$), 4.63 (dtdd, *J* = 8.7, 6.9, 5.1, 3.6 Hz, 1H, $H_2C$=C($CH_3$)-$CH_2C\underline{H}O$(P)$CH_2$), 4.08 (q, *J* = 6.8 Hz, 2H, (P)$OC\underline{H}_2CH_2CH_2CH_2CH$=$CH_2$), 2.62 (dd, *J* = 14.2, 7.0 Hz, 1H, $H_2C$=C($CH_3$)-$C\underline{H}_aH_bCHO$(P)$CH_2$), 2.55 (dd, *J* = 14.2, 6.9 Hz, 1H, $H_2C$=C($CH_3$)-$C\underline{H}_aH_bCHO$(P)$CH_2$), 2.40–2.30 (m, 2H, $H_2C$=C($CH_3$)-$CH_a\underline{H}_bCHO$(P)$CH_2$, $H_2C$=C($CH_3$)-$CH_a\underline{H}_bCHO$(P)$CH_2$), 2.09 (q, *J* = 7.1 Hz, 2H, (P)$OCH_2CH_2C\underline{H}_2CH$=$CH_2$), 2.01 (dddd, *J* = 13.5, 8.6, 5.0, 1.3 Hz, 1H, $H_2C$=C($CH_3$)$CH_2$-CHO(P)$C\underline{H}_aH_bCHO$[P]), 1.86 (dddd, *J* = 14.7, 5.2, 3.5, 1.8 Hz, 1H, $H_2C$=C($CH_3$)$CH_2$-CHO(P)$CH_a\underline{H}_bCHO$[P]), 1.76 (d, *J* = 5.9 Hz, 6H, (P)$OCH_2CH_2CH_2C(C\underline{H}_3)$=$CH_2$, (P)$OCH_2CH_2CH_2C(C\underline{H}_3)$=$CH_2$), 1.74–1.67 (m, 2H, $H_2C$=CH-$CH_2$-$CH_2$-$C\underline{H}_2$-CHO(P)), 1.49 (p, *J* = 7.5 Hz, 2H, $H_2C$=CH-$CH_2$-$C\underline{H}_2$-$CH_2$-CHO(P));

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ ppm 140.3 (C), 140.2 (C), 138.2 (CH), 114.9 ($CH_2$), 114.18 ($CH_2$), 114.17 ($CH_2$), 75.8 (d, $J_{CP}$ = 6.8 Hz, CH), 74.5 (d, $J_{CP}$ = 6.5 Hz, CH), 67.7 (d, $J_{CP}$ = 5.9 Hz, $CH_2$), 43.7 (d, $J_{CP}$ = 7.3 Hz, $CH_2$), 42.7 (d, $J_{CP}$ = 3.2 Hz, $CH_2$), 33.4 (d, $J_{CP}$ = 6.8 Hz, $CH_2$), 33.1 ($CH_2$), 29.7 (d, $J_{CP}$ = 6.7 Hz, $CH_2$), 24.8 ($CH_2$), 22.6 ($CH_3$), 22.3 ($CH_3$);

**$^{31}$P NMR (162 MHz, $CDCl_3$)** δ ppm –6.67 (s);

**HRMS (TOF MS ES+)** calcd for $(C_{17}H_{29}O_4P)_2Na$ $(2M+Na)^+$ 679.3505; found 679.3520.

**(1*S*,10*R*,12*R*,*Z*)-8-methyl-12-(2-methylallyl)-2,13,14-trioxa-1-phosphabicyclo[8.3.1]-tetradec-7-ene 1-oxide** (**2.16.2**):



(*R*,*R*)-**2.16.2**

Following General Procedure 2, triene **2.16.1** (20.0 mg, 0.0609 mmol) was exposed to G-II catalyst (7 mol %, over 9 hours) in refluxing $CH_2Cl_2$ to provide the corresponding bicyclic phosphate **2.16.2** (14.8 mg, 0.0493 mmol, 81%) as a colorless oil.

**FTIR (neat)**: 2963, 2916, 1855, 1443, 1377, 1103, 1072, 1053, 1020, 1005, 978, 943, 924, 897, 793, 762, 544 $cm^{-1}$;

**Optical Rotation** $[\alpha]_D$ = +37.3 (*c* 0.15, $CHCl_3$);

**$^1$H NMR (500 MHz, $CDCl_3$)** δ ppm 5.18 (ddd, *J* = 12.0, 3.4, 1.7 Hz, 1H, (P)OCHCH$_2$C(CH$_3$)=C$\underline{H}$CH$_2$), 4.93–4.83 (m, 2H, (P)OC$\underline{H}$CH$_2$C(CH$_3$)=C$\underline{H}_a$H$_b$), 4.83–4.76 (m, 2H, (P)OCHCH$_2$C(CH$_3$)=CH$_a\underline{H}_b$, (P)OC$\underline{H}$CH$_2$C(CH$_3$)=CHCH$_2$), 4.74–4.68 (m, 1H, (P)OC$\underline{H}_a$H$_b$CH$_2$CH$_2$CH$_2$CH=C(CH$_3$)CH$_2$), 3.89 (dddd, *J* = 19.0, 11.7, 10.6, 1.2 Hz, 1H, (P)OCH$_a\underline{H}_b$CH$_2$CH$_2$CH$_2$CH=C(CH$_3$)CH$_2$), 3.31 (dd, *J* = 14.1, 13.0 Hz, 1H, (P)OCHC$\underline{H}_a$H$_b$C(CH$_3$)=CHCH$_2$), 2.60 (dddd, *J* = 14.2, 11.9, 9.4, 6.3 Hz, 1H, (P)OCH$_2$CH$_2$CH$_2$C$\underline{H}_a$H$_b$CH=C(CH$_3$)CH$_2$), 2.51 (dd, *J* = 14.2, 6.7 Hz, 1H, (P)OCHC$\underline{H}_a$H$_b$C(CH$_3$)=CH$_2$), 2.29 (dddd, *J* = 14.3, 6.5, 2.8, 1.0 Hz, 1H, (P)OCHCH$_a\underline{H}_b$C(CH$_3$)=CH$_2$), 2.25–2.16 (m, 1H, H$_2$C=C(CH$_3$)CH$_2$-CHO(P)C$\underline{H}_a$H$_b$CHO[P]), 2.03–1.96 (m, 1H, (P)OCH$_2$CH$_2$CH$_2$CH$_a\underline{H}_b$CH=C(CH$_3$)CH$_2$), 1.90–1.81 (m, 1H, (P)OCH$_2$C$\underline{H}_a$H$_b$CH$_2$CH$_2$CH=C(CH$_3$)CH$_2$), 1.79 (dt, *J* = 3.9, 1.1 Hz, 6H, (P)OCHCH$_2$C(C$\underline{H}_3$)=CHCH$_2$, (P)OCHCH$_2$C(C$\underline{H}_3$)=CH$_2$), 1.72–1.62 (m, 4H, (P)OCHCH$_a\underline{H}_b$C(CH$_3$)=CHCH$_2$, H$_2$C=C(CH$_3$)CH$_2$-CHO(P)CH$_a\underline{H}_b$CHO[P],

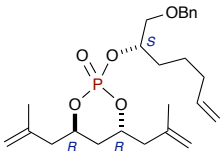
(P)$OCH_2CH_2C\underline{H}_2CH_2CH=C(CH_3)CH_2$), 1.59–1.53 (m, 1H, (P)$OCH_2CH_a\underline{H}_bCH_2CH_2CH=C(CH_3)CH_2$);

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ ppm 140.1 (C), 130.2 (C), 128.8 (CH), 114.2 ($CH_2$), 75.8 (d, $J_{CP}$ = 8.0 Hz, CH), 74.0 (d, $J_{CP}$ = 6.9 Hz, CH), 71.6 (d, $J_{CP}$ = 6.6 Hz, $CH_2$), 44.4 (d, $J_{CP}$ = 8.8 Hz, $CH_2$), 36.0 ($CH_2$), 34.7 (d, $J_{CP}$ = 7.0 Hz, $CH_2$), 28.6 ($CH_2$), 27.4 ($CH_2$), 26.0 ($CH_2$), 22.9 ($CH_3$), 22.2 ($CH_3$);

**$^{31}$P NMR (162 MHz, $CDCl_3$)** δ ppm –7.95 (td, $J_{PH}$ = 20.5, 9.7 Hz);

**HRMS (TOF MS ES+)** calcd for $(C_{15}H_{25}O_4P)_2Na$ $(2M+Na)^+$ 623.2879; found 623.2889.

**(4*R*,6*R*)-2-(((*S*)-1-(benzyloxy)hept-6-en-2-yl)oxy)-4,6-bis(2-methylallyl)-1,3,2-dioxaphosphinane 2-oxide** (**2.16.3**):




(*S,R,R*)-**2.16.3**

Following General Procedure 1, monochlorophosphate (*R,R*)-**2.13.2** (0.180 g, 0.679 mmol) and alcohol (*S*)-**2.15.3** (0.137 g, 0.622 mmol) were converted into **2.16.3** (0.158 g, 0.352 mmol, 62%) which was isolated as a colorless oil.

**FTIR (neat)**: 2936, 2862, 1452, 1375, 1366, 1286, 1207, 1003, 1101, 1070, 1003, 970, 8945, 812, 739, 698, 553 $cm^{-1}$;

**Optical Rotation** $[\alpha]_D$ = +34.9 (*c* = 0.93, $CHCl_3$);

**$^1$H NMR (500 MHz, $CDCl_3$)** δ ppm 7.34 (d, *J* = 3.7 Hz, 4H, aromatic C-H), 7.32–7.28 (m, 1H, aromatic C-H), 5.78 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H, $H_2C=C\underline{H}$-$CH_2$-$CH_2$-$CH_2$-CHO(P)$CH_2$OBn), 5.00 (dq, *J* = 17.1, 1.7 Hz, 1H, $\underline{H}_aH_bC$=CH-$CH_2$-$CH_2$-$CH_2$-

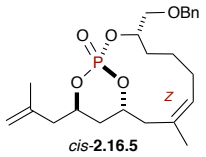
CHO(P)$CH_2$OBn), 4.95 (ddt, *J* = 10.2, 2.2, 1.2 Hz, 1H, $H_a\underline{H_b}C$=CH-$CH_2$-$CH_2$-$CH_2$-CHO(P)$CH_2$OBn), 4.84 (dt, *J* = 14.7, 1.6 Hz, 2H, $\underline{H_2}C$=C($CH_3$)-$CH_2$CHO(P)$CH_2$), 4.77–4.66 (m, 4H, $\underline{H_2}C$=C($CH_3$)-$CH_2$CHO(P)$CH_2$, $H_2C$=C($CH_3$)-$CH_2C\underline{H}$O(P)$CH_2$, $H_2C$=C($CH_3$)-$CH_2C\underline{H}$O(P)$CH_2$), 4.62–4.51 (m, 3H, $H_2C$=CH-$CH_2$-$CH_2$-$CH_2$-$C\underline{H}$O(P)$CH_2$OBn, O$C\underline{H_2}$Ph), 3.58 (dd, *J* = 4.8, 1.2 Hz, 2H, -$C\underline{H_2}$OBn), 2.63 (ddd, *J* = 14.2, 7.1, 1.2 Hz, 1H, $H_2C$=C($CH_3$)-$C\underline{H_a}H_b$CHO(P)$CH_2$), 2.49 (dd, *J* = 14.2, 6.4 Hz, 1H, $H_2C$=C($CH_3$)-$C\underline{H_a}H_b$CHO(P)$CH_2$), 2.36 (dd, *J* = 14.1, 7.4 Hz, 1H, $H_2C$=C($CH_3$)-$CH_a\underline{H_b}$CHO(P)$CH_2$), 2.29 (ddt, *J* = 14.2, 7.4, 1.3 Hz, 1H, $H_2C$=C($CH_3$)-$CH_a\underline{H_b}$CHO(P)$CH_2$), 2.07 (qdd, *J* = 6.4, 2.9, 1.4 Hz, 2H, $H_2C$=CH-$C\underline{H_2}$-$CH_2$-$CH_2$-CHO(P)$CH_2$OBn), 1.96 (dddd, *J* = 14.5, 8.1, 4.9, 1.4 Hz, 1H, $H_2C$=C($CH_3$)$CH_2$-CHO(P)$C\underline{H_a}H_b$CHO[P]), 1.86 (dddd, *J* = 14.6, 5.4, 3.8, 1.7 Hz, 1H, $H_2C$=C($CH_3$)$CH_2$-CHO(P)$CH_a\underline{H_b}$CHO[P]), 1.75 (s, 3H, $H_2C$=C($C\underline{H_3}$)$CH_2$-CHO(P)), 1.74–1.70 (m, 2H, $H_2C$=CH-$CH_2$-$CH_2$-$C\underline{H_2}$-CHO(P)$CH_2$OBn), 1.69 (t, *J* = 1.2 Hz, 3H, $H_2C$=C($C\underline{H_3}$)$CH_2$-CHO(P)), 1.57–1.41 (m, 2H, $H_2C$=CH-$CH_2$-$C\underline{H_2}$-$CH_2$-CHO(P)$CH_2$OBn);

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ ppm 140.5 (C), 140.3 (C), 138.3 (CH), 137.9 (C), 128.4 (2 x CH), 127.7 (CH), 127.6 (2 x CH), 114.8 ($CH_2$), 114.12 ($CH_2$), 114.11 ($CH_2$), 77.9 (d, *J* = 6.2 Hz, CH), 76.0 (d, *J* = 6.8 Hz, CH), 74.3 (d, *J* = 6.5 Hz, CH), 73.2 ($CH_2$), 71.9 (d, *J* = 4.5 Hz, $CH_2$), 43.8 (d, *J* = 7.5 Hz, $CH_2$), 42.8 (d, *J* = 3.6 Hz, $CH_2$), 33.5 ($CH_2$), 33.3 (d, *J* = 6.8 Hz, $CH_2$), 31.7 (d, *J* = 4.5 Hz, $CH_2$), 24.2 ($CH_2$), 22.6 ($CH_3$), 22.4 ($CH_3$);

**$^{31}$P NMR (162 MHz, $CDCl_3$)** δ ppm –7.07 (dt, $J_{PH}$ = 13.1, 6.0 Hz);

**HRMS (TOF MS ES+)** calcd for $(C_{25}H_{37}O_5P)_2Na$ $(2M+Na)^+$ 919.4655; found 919.4643.

**(1*S*,3*S*,10*R*,12*R*,*Z*)-3-((benzyloxy)methyl)-8-methyl-12-(2-methylallyl)-2,13,14-trioxa-1-phosphabicyclo[8.3.1]tetradec-7-ene 1-oxide** (*cis*-**2.16.5**):




*cis*-**2.16.5**

Following General Procedure 2, triene **2.16.3** (30.0 mg, 0.0669 mmol) was exposed to G-II catalyst (4 mol %, over 5 hours) in refluxing $CH_2Cl_2$ to provide the corresponding bicyclic phosphate *cis*-**2.16.5** (19.2 mg, 0.0457 mmol, 68%) as a colorless oil.

**FTIR (neat)**: 2963, 2936, 2920, 2862, 1452, 1377, 1283, 1103, 1074, 1003, 972, 918, 797, 698, 550 $cm^{-1}$; $[\alpha]_D$ = +32.4 (*c* 0.17, $CHCl_3$);

**$^1$H NMR (500 MHz, $CDCl_3$)** δ ppm 7.37–7.33 (m, 4H, Aromatic C-H), 7.32–7.28 (m, 1H, Aromatic C-H), 5.20 (ddt, *J* = 11.8, 3.2, 1.5 Hz, 1H, (P)OCHC$H_2$C($CH_3$)=C$\underline{H}$C$H_2$), 5.05 (ddtd, *J* = 10.0, 7.7, 4.9, 3.0 Hz, 1H, (P)OC$\underline{H}$C$H_2$C($CH_3$)=CHC$H_2$), 4.88 (ddt, *J* = 15.8, 9.5, 4.4 Hz, 1H, (P)OC$\underline{H}$C$H_2$C($CH_3$)=C$H_2$), 4.83–4.76 (m, 3H, (P)OCHC$H_2$C($CH_3$)=C$\underline{H_2}$, C$H_2$($CH_3$)C=CHC$H_2$C$H_2$C$H_2$C$\underline{H}$O(P)C$H_2$OBn), 4.59 (d, *J* = 12.0 Hz, 1H, -OC$\underline{H_a}$$H_b$Ph), 4.56 (d, *J* = 12.0 Hz, 1H, -OC$H_a$$\underline{H_b}$Ph), 3.66 (dd, *J* = 10.4, 7.3 Hz, 1H, C$H_2$CHO(P)C$\underline{H_a}$$H_b$OBn), 3.56 (ddd, *J* = 10.4, 5.2, 1.9 Hz, 1H, C$H_2$CHO(P)C$H_a$$\underline{H_b}$OBn), 3.29 (t, *J* = 13.6 Hz, 1H, (P)OCHC$\underline{H_a}$$H_b$C($CH_3$)=CHC$H_2$), 2.58–2.50 (m, 1H, C$H_2$($CH_3$)C=CHC$\underline{H_a}$$H_b$C$H_2$C$H_2$CHO(P)), 2.47 (dd, *J* = 14.4, 7.0 Hz, 1H, (P)OCHC$\underline{H_a}$$H_b$C($CH_3$)=C$H_2$), 2.28 (dddd, *J* = 14.5, 6.2, 3.0, 1.0 Hz, 1H, (P)OCHC$H_a$$\underline{H_b}$C($CH_3$)=C$H_2$), 2.24–2.16 (m, 1H, $H_2$C=C($CH_3$)C$H_2$-CHO(P)C$\underline{H_a}$$H_b$CHO[P]), 1.94 (ddt, *J* = 15.5, 5.7, 2.9 Hz, 2H, C$H_2$($CH_3$)C=CHC$H_a$$\underline{H_b}$C$H_2$C$H_2$CHO(P), C$H_2$($CH_3$)C=CHC$H_2$C$H_2$C$\underline{H_a}$$H_b$CHO(P)C$H_2$OBn), 1.80–1.72 (m, 7H,

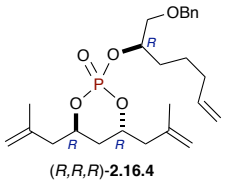
$CH_2(CH_3)C{=}CHCH_2C\underline{H}_aH_bCH_2CHO(P)CH_2OBn$, $(P)OCHCH_2C(C\underline{H}_3){=}CHCH_2$, $(P)OCHCH_2C(C\underline{H}_3){=}CH_2$), 1.72–1.65 (m, 3H, $(P)OCHCH_a\underline{H}_bC(CH_3){=}CHCH_2$, $H_2C{=}C(CH_3)CH_2$-CHO(P)$CH_a\underline{H}_bCHO$[P], $CH_2(CH_3)C{=}CHCH_2CH_2CH_a\underline{H}_bCHO(P)CH_2OBn$), 1.42 (ddtd, $J$ = 14.6, 12.5, 5.1, 2.7 Hz, 1H, $CH_2(CH_3)C{=}CHCH_2CH_a\underline{H}_bCH_2CHO(P)CH_2OBn$);

**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ ppm 140.2 (C), 138.1 (C), 130.3 (C), 128.6 (CH), 128.3 (2 x CH), 127.53 (CH), 127.52 (2 x CH), 114.0 ($CH_2$), 78.1 (d, $J_{CP}$ = 6.9 Hz, CH), 75.7 (d, $J_{CP}$ = 8.1 Hz, CH), 73.9 (d, $J_{CP}$ = 6.9 Hz, CH), 72.9 ($CH_2$), 70.5 (d, $J_{CP}$ = 6.3 Hz, $CH_2$), 44.3 (d, $J_{CP}$ = 8.9 Hz, $CH_2$), 36.0 ($CH_2$), 34.7 (d, $J_{CP}$ = 6.7 Hz, $CH_2$), 28.3 (d, $J_{CP}$ = 2.3 Hz, $CH_2$), 26.5 ($CH_2$), 23.3 ($CH_2$), 22.8 ($CH_3$), 22.2 ($CH_3$);

**$^{31}$P NMR (162 MHz, $CDCl_3$)** δ ppm –8.71 (dd, $J_{PH}$ = 23.2, 9.4 Hz);

**HRMS (TOF MS ES+)** calcd for $(C_{23}H_{33}O_5P)_2Na$ $(2M+Na)^+$ 863.4029; found 863.4021.

**(4*R*,6*R*)-2-(((*R*)-1-(benzyloxy)hept-6-en-2-yl)oxy)-4,6-bis(2-methylallyl)-1,3,2-dioxaphosphinane 2-oxide** (**2.16.4**):



(*R,R,R*)-**2.16.4**

Following General Procedure 1, monochlorophosphate (*R,R*)-**2.13.2** (0.180 g, 0.679 mmol) and alcohol (*R*)-**2.15.3** (0.137 g, 0.622 mmol) were converted into **2.16.4** (0.118 g, 0.263 mmol, 47%) which was isolated as a colorless oil.

**FTIR (neat)**: 2936, 2860, 1452, 1377, 1366, 1285, 1101, 1069, 1003, 897, 847, 808, 739, 698, 550 $cm^{-1}$;

**Optical Rotation** $[\alpha]_D$ = +30.5 (*c* 1.00, $CHCl_3$);

**$^1$H NMR (500 MHz, $CDCl_3$)** δ ppm 7.34 (d, *J* = 4.4 Hz, 4H, aromatic C-H), 7.31–7.27 (m, 1H, aromatic C-H), 5.79 (ddt, *J* = 16.9, 10.1, 6.7 Hz, 1H, $H_2C$=C<u>H</u>-$CH_2$-$CH_2$-$CH_2$-CHO(P)$CH_2$OBn), 5.02 (dq, *J* = 17.1, 1.6 Hz, 1H, <u>H</u>$_a$H$_b$C=CH-$CH_2$-$CH_2$-$CH_2$-CHO(P)$CH_2$OBn), 4.96 (ddt, *J* = 10.2, 2.2, 1.2 Hz, 1H, H$_a$<u>H</u>$_b$C=CH-$CH_2$-$CH_2$-$CH_2$-CHO(P)$CH_2$OBn), 4.87 (t, *J* = 1.7 Hz, 1H, <u>H</u>$_a$H$_b$C=C($CH_3$)-$CH_2$CHO(P)$CH_2$), 4.85–4.83 (m, 1H, H$_a$<u>H</u>$_b$C=C($CH_3$)-$CH_2$CHO(P)$CH_2$), 4.79 (dq, *J* = 1.9, 0.9 Hz, 1H, <u>H</u>$_a$H$_b$C=C($CH_3$)-$CH_2$CHO(P)$CH_2$), 4.76–4.70 (m, 2H, H$_a$<u>H</u>$_b$C=C($CH_3$)-$CH_2$CHO(P)$CH_2$, $H_2C$=C($CH_3$)-$CH_2$C<u>H</u>O(P)$CH_2$), 4.67–4.57 (m, 3H, $H_2C$=C($CH_3$)-$CH_2$C<u>H</u>O(P)$CH_2$, $H_2C$=CH-$CH_2$-$CH_2$-$CH_2$-C<u>H</u>O(P)$CH_2$OBn, OC<u>H</u>$_a$H$_b$Ph), 4.53 (d, *J* = 12.0 Hz, 1H, OCH$_a$<u>H</u>$_b$Ph), 3.61 (t, *J* = 4.9 Hz, 2H, $H_2C$=CH-$CH_2$-$CH_2$-$CH_2$-CHO(P)C<u>H</u>$_2$OBn), 2.64–2.51 (m, 2H, $H_2C$=C($CH_3$)-C<u>H</u>$_2$CHO(P)$CH_2$), 2.40–2.31 (m, 2H, $H_2C$=C($CH_3$)-C<u>H</u>$_2$CHO(P)$CH_2$), 2.09 (dtdt, *J* = 7.9, 6.5, 3.6, 1.3 Hz, 2H, $H_2C$=CH-C<u>H</u>$_2$-$CH_2$-$CH_2$-CHO(P)$CH_2$OBn), 1.98 (dddd, *J* = 14.4, 8.0, 4.9, 1.5 Hz, 1H, $H_2C$=C($CH_3$)$CH_2$-CHO(P)C<u>H</u>$_a$H$_b$CHO[P]), 1.89 (dddd, *J* = 14.6, 5.6, 3.9, 1.7 Hz, 1H, $H_2C$=C($CH_3$)$CH_2$-CHO(P)CH$_a$<u>H</u>$_b$CHO[P]), 1.78–1.69 (m, 8H, $H_2C$=C(C<u>H</u>$_3$)-$CH_2$CHO(P)$CH_2$, $H_2C$=C(C<u>H</u>$_3$)-$CH_2$CHO(P)$CH_2$, $H_2C$=CH-$CH_2$-$CH_2$-C<u>H</u>$_2$-CHO(P)$CH_2$OBn), 1.57–1.41 (m, 2H, $H_2C$=CH-$CH_2$-C<u>H</u>$_2$-$CH_2$-CHO(P)$CH_2$OBn);

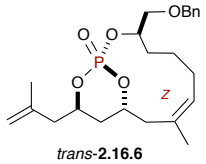
**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ ppm 140.4 (C), 140.3 (C), 138.2 (CH), 138.1 (C), 128.3 (2 x CH), 127.60 (2 x CH), 127.57 (CH), 114.9 ($CH_2$), 114.20 ($CH_2$), 114.15 ($CH_2$), 78.2 (d, *J* = 6.3 Hz, CH), 75.6 (d, *J* = 6.6 Hz, CH), 74.6 (d, *J* = 6.7 Hz, CH), 73.2 ($CH_2$), 71.7 (d, *J* = 4.1 Hz, $CH_2$), 43.7 (d, *J* = 7.1 Hz, $CH_2$), 43.0 (d, *J* = 4.1 Hz, $CH_2$), 33.4 ($CH_2$),

33.3 (d, $J$ = 6.7 Hz, $CH_2$), 31.6 (d, $J$ = 4.9 Hz, $CH_2$), 24.3 ($CH_2$), 22.6 ($CH_3$), 22.3 ($CH_3$);

**$^{31}$P NMR (162 MHz, $CDCl_3$)** δ ppm –6.90 (dt, $J_{PH}$ = 13.5, 6.8 Hz);

**HRMS (TOF MS ES+)** calcd for $(C_{25}H_{37}O_5P)_2Na$ $(2M+Na)^+$ 919.4655; found 919.4681.

**(1*S*,3*R*,10*R*,12*R*,*Z*)-3-((benzyloxy)methyl)-8-methyl-12-(2-methylallyl)-2,13,14-trioxa-1-phosphabicyclo[8.3.1]tetradec-7-ene 1-oxide** (*trans*-**2.16.6**):




*trans*-**2.16.6**

Following General Procedure 2, triene **2.16.4** (20.0 mg, 0.0446 mmol) was exposed to G-II catalyst (2 mol %, over 3 hours) in refluxing $CH_2Cl_2$ to provide the corresponding bicyclic phosphate *trans*-**2.16.6** (13.5 mg, 0.0321 mmol, 72%) as a white, crystalline solid, which was recrystallized via vapor-diffusion method (EtOAc:Hexanes) to afford X-ray quality crystals for X-ray crystallographic analysis (which confirmed stereochemical olefin assignment as *Z*).[10]

**FTIR (neat)**: 2961, 2924, 2858, 1452, 1378, 1273, 1105, 1094, 1076, 1020, 974, 951, 908, 783, 739, 698, 542 $cm^{-1}$;

**Optical Rotation** $[\alpha]_D$ = +54.4 (*c* 0.86, $CHCl_3$);

**$^1$H NMR (500 MHz, $CDCl_3$)** δ ppm 7.38–7.32 (m, 4H, Aromatic C-H), 7.29 (dt, $J$ = 6.8, 3.0 Hz, 1H, Aromatic C-H), 5.29 (dd, $J$ = 12.3, 4.0 Hz, 1H, $CH_2$(P)OCHC$H_2$C($CH_3$)=C$\underline{H}$C$H_2$), 4.89–4.82 (m, 2H, $CH_2$(P)OC$\underline{H}$C$H_2$C($CH_3$)=CHC$H_2$, $CH_2$(P)OCHC$H_2$C($CH_3$)=C$\underline{H_a}H_b$), 4.80 (dd, $J$ = 2.1, 1.0 Hz, 1H, $CH_2$(P)OCHC$H_2$C($CH_3$)=C$H_a\underline{H_b}$), 4.76 (ddd, $J$ = 11.3, 6.5, 2.5 Hz, 1H, $CH_2$(P)OC$\underline{H}$C$H_2$C($CH_3$)=C$H_2$), 4.61 (d, $J$ = 11.9 Hz, 1H, -OC$\underline{H_a}H_b$Ph), 4.56 (d, $J$ = 11.9

Hz, 1H, -OCH$_a$H$_b$Ph), 4.31 (dddd, *J* = 14.0, 11.5, 6.8, 4.6 Hz, 1H, CH$_2$(CH$_3$)C=CHCH$_2$CH$_2$CH$_2$CHO(P)CH$_2$OBn), 3.63 (dd, *J* = 10.8, 6.6 Hz, 1H, CH$_2$CHO(P)CH$_a$H$_b$OBn), 3.58 (ddd, *J* = 10.7, 3.9, 2.4 Hz, 1H, CH$_2$CHO(P)CH$_a$H$_b$OBn), 3.12–3.05 (m, 1H, CH$_2$(P)OCHCH$_a$H$_b$C(CH$_3$)=CHCH$_2$), 2.57 (dd, *J* = 14.2, 6.6 Hz, 1H, CH$_2$(P)OCHCH$_a$H$_b$C(CH$_3$)=CH$_2$), 2.50 (ddd, *J* = 15.1, 11.3, 6.2 Hz, 1H, H$_2$C=C(CH$_3$)CH$_2$-CHO(P)CH$_a$H$_b$CHO[P]), 2.35 (ddt, *J* = 14.3, 6.8, 1.3 Hz, 1H, CH$_2$(P)OCHCH$_a$H$_b$C(CH$_3$)=CH$_2$), 2.32–2.25 (m, 1H, CH$_2$(CH$_3$)C=CHCH$_a$H$_b$CH$_2$CH$_2$CHO(P)CH$_2$OBn), 1.93–1.80 (m, 3H, H$_2$C=C(CH$_3$)CH$_2$-CHO(P)CH$_a$H$_b$CHO[P], CH$_2$(CH$_3$)C=CHCH$_a$H$_b$CH$_2$CH$_a$H$_b$CHO(P)CH$_2$OBn), 1.76 (dt, *J* = 10.3, 1.4 Hz, 7H, CH$_2$(P)OCHCH$_a$H$_b$C(CH$_3$)=CHCH$_2$, CH$_2$(P)OCHCH$_2$C(CH$_3$)=CHCH$_2$, CH$_2$(P)OCHCH$_2$C(CH$_3$)=CH$_2$), 1.53 (dddd, *J* = 25.2, 12.3, 6.8, 3.4 Hz, 3H, CH$_2$(CH$_3$)C=CHCH$_2$CH$_2$CH$_a$H$_b$CHO(P)CH$_2$OBn);

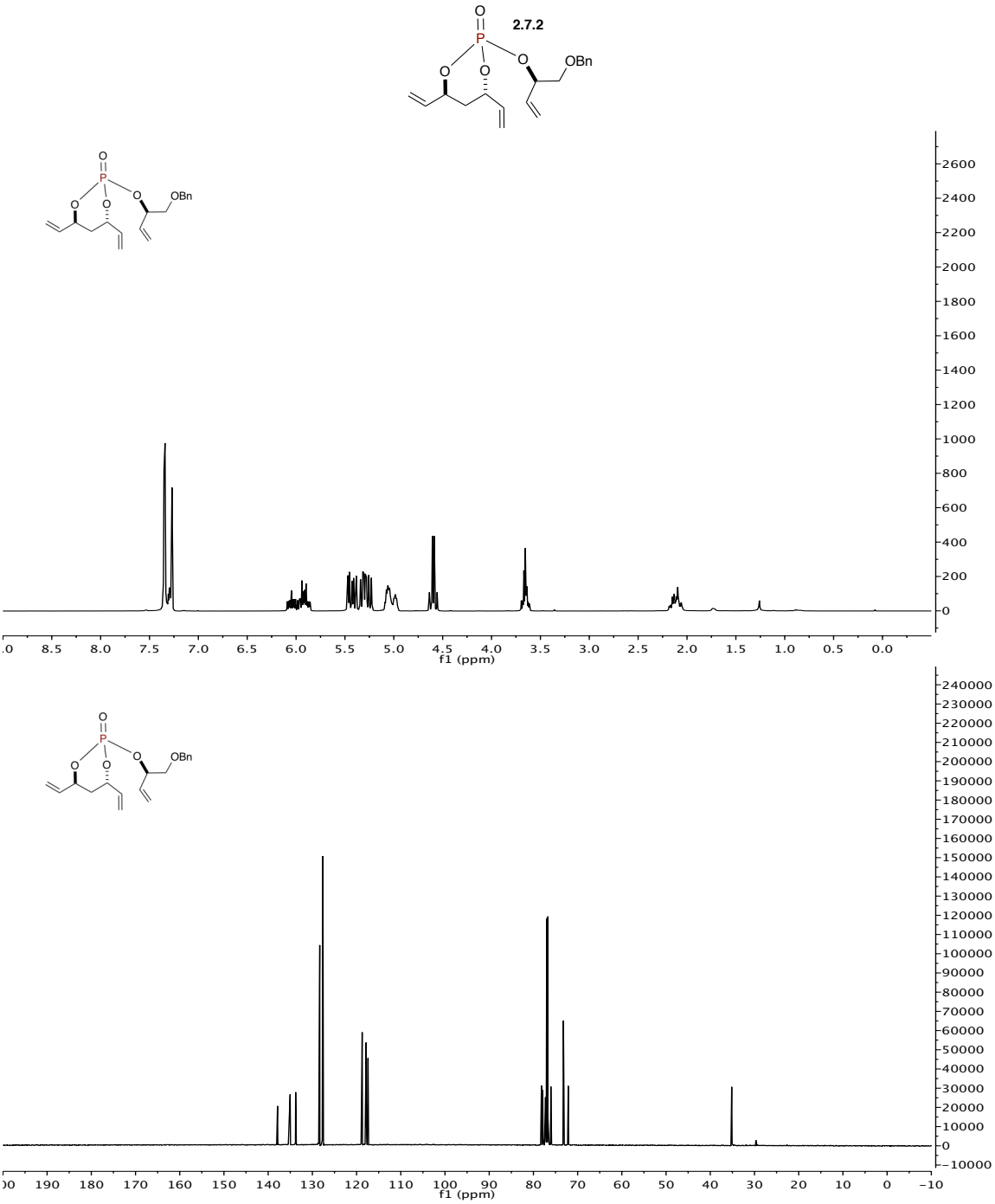
**$^{13}$C NMR (126 MHz, CDCl$_3$)** δ ppm 140.3 (C), 138.1 (C), 130.1 (C), 128.6 (CH), 128.3 (2 x CH), 127.7 (2 x CH), 127.6 (CH), 114.1 (CH$_2$), 77.1 (d, $J_{CP}$ = 8.6 Hz, CH), 75.8 (d, $J_{CP}$ = 6.1 Hz, CH), 74.3 (d, $J_{CP}$ = 6.4 Hz, CH), 73.6 (CH$_2$), 72.4 (d, $J_{CP}$ = 7.0 Hz, CH$_2$), 44.5 (d, $J_{CP}$ = 4.9 Hz, CH$_2$), 37.4 (d, $J_{CP}$ = 4.2 Hz, CH$_2$), 34.8 (d, $J_{CP}$ = 11.8 Hz, CH$_2$), 29.1 (d, $J_{CP}$ = 1.9 Hz, CH$_2$), 25.0 (CH$_2$), 23.9 (CH$_2$), 23.0 (CH$_3$), 22.8 (CH$_3$);

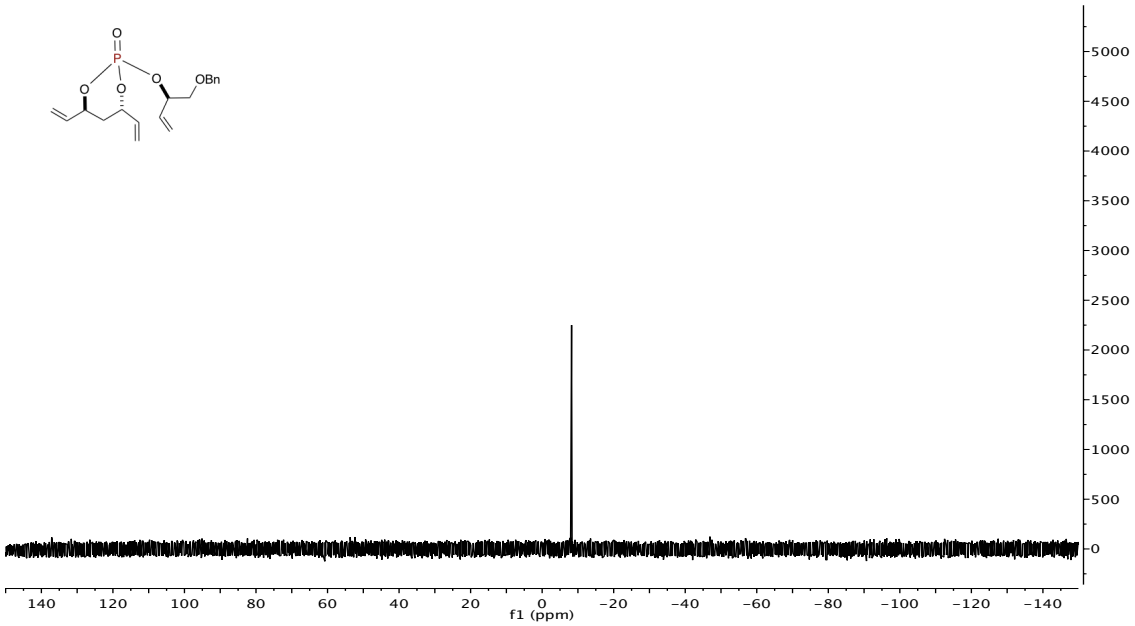
**$^{31}$P NMR (162 MHz, CDCl$_3$)** δ ppm –9.90 (d, $J_{PH}$ = 9.8 Hz);

**HRMS (TOF MS ES+)** calcd for (C$_{23}$H$_{33}$O$_5$P)$_2$Na (2M+Na)$^+$ 863.4029; found 863.4023.

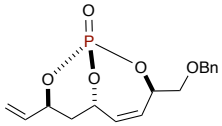
### 5.1.3 NMR Spextra

**(4*S*,6*S*)-2-(((*R*)-1-(benzyloxy)but-3-en-2-yl)oxy)-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide (2.7.2):**

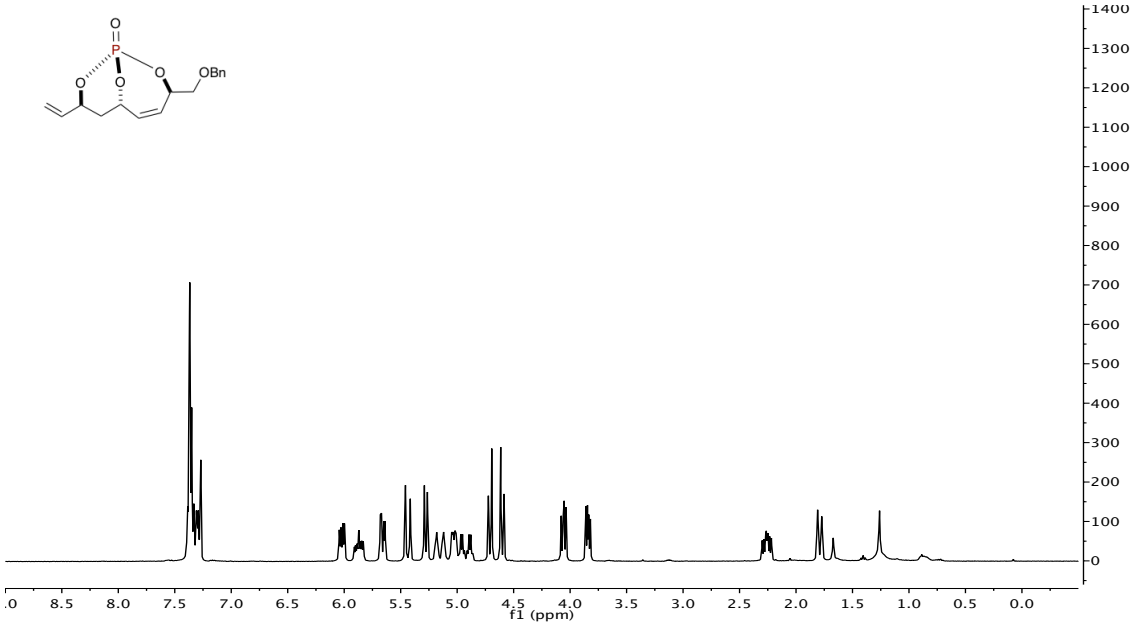


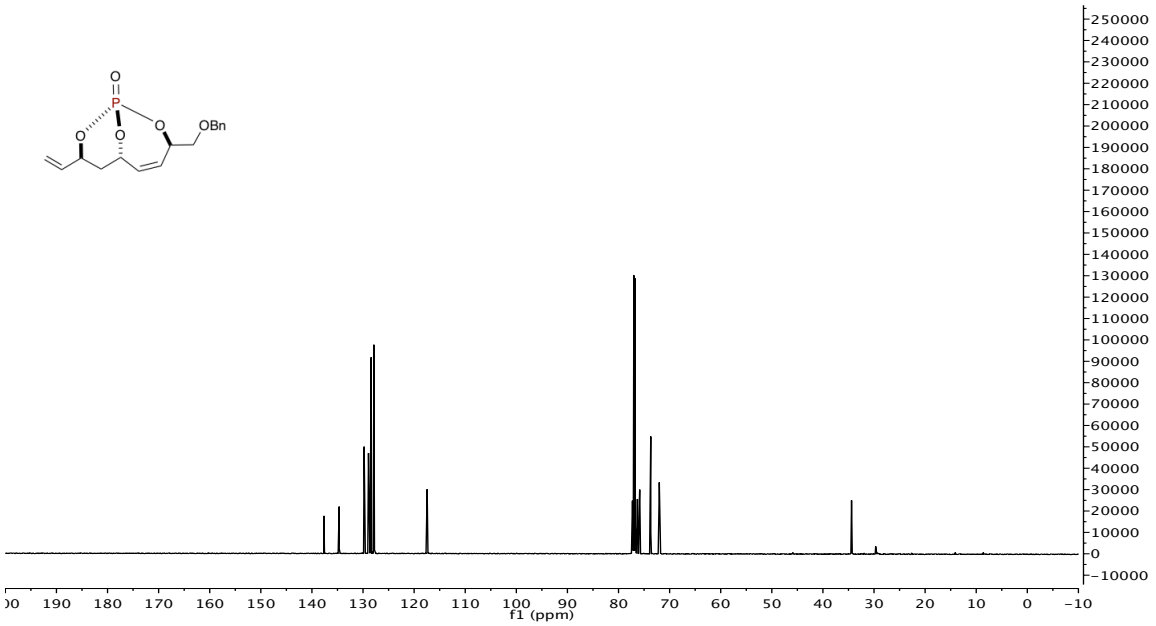



**(1*S*,3*R*,6*S*,8*S*)-3-((benzyloxy)methyl)-8-vinyl-2,9,10-trioxa-1-phosphabicyclo[4.3.1]-dec-4-ene 1-oxide (*trans*-2.7.4):**




*trans*-**2.7.4**

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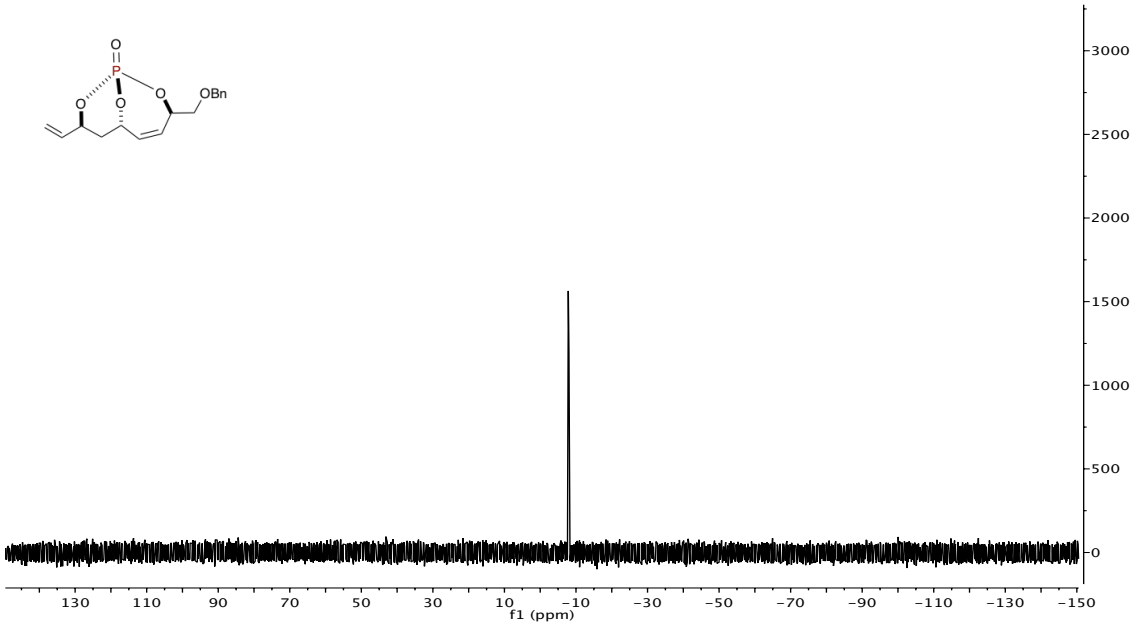
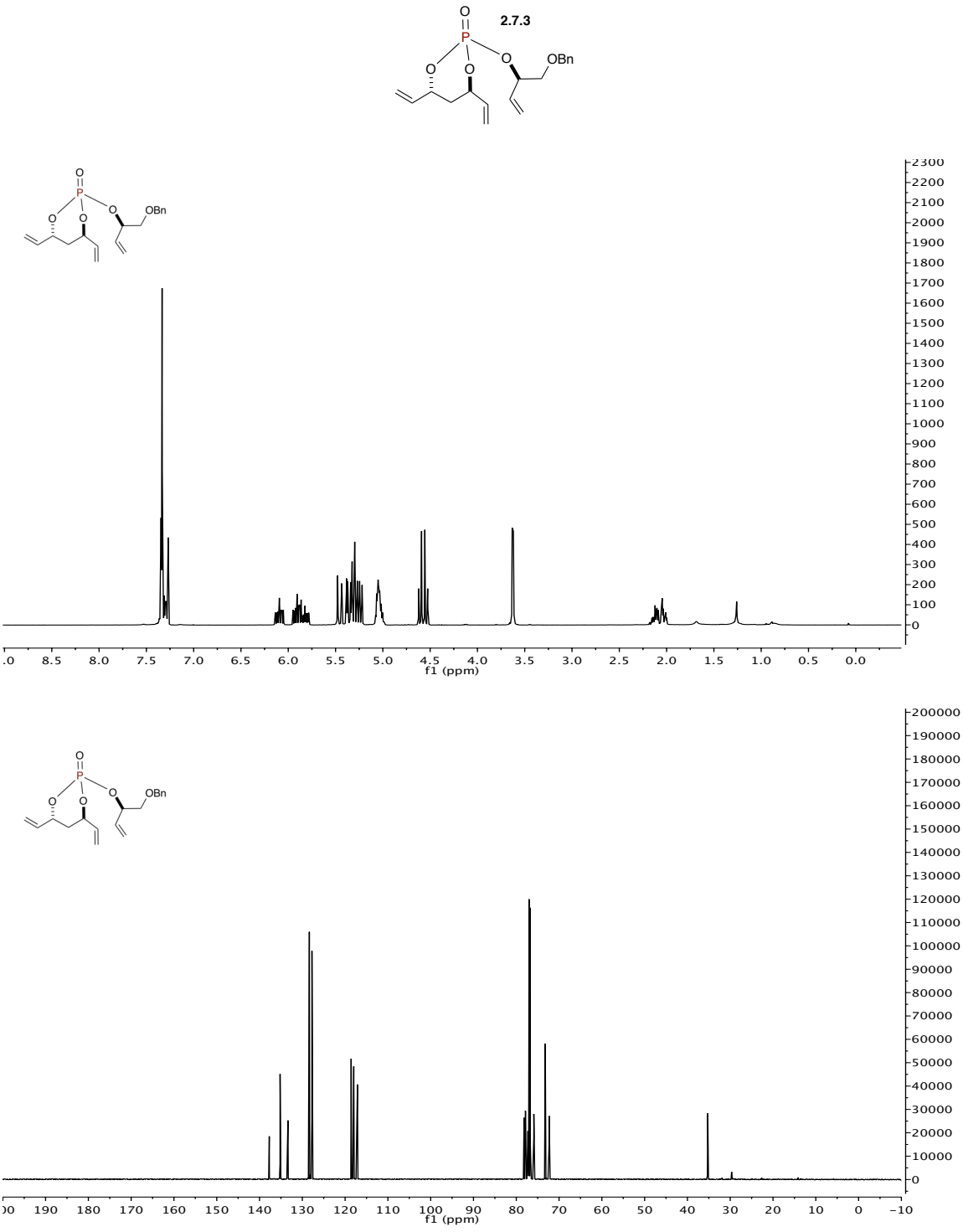
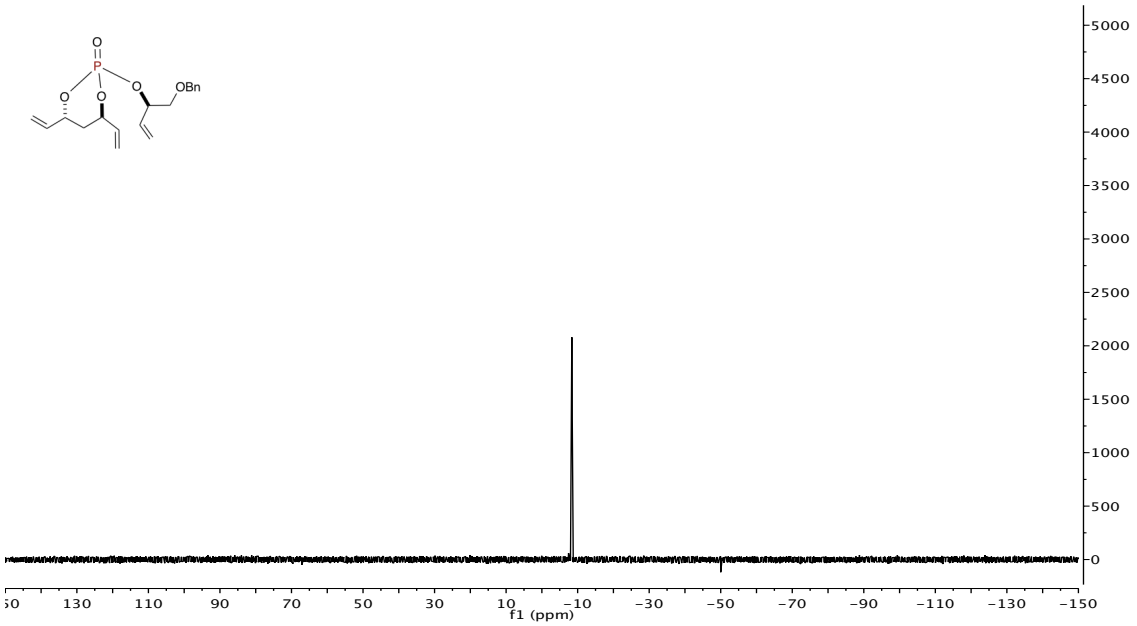
OBn
250000
240000
230000
220000
210000
200000
190000
180000
170000
160000
150000
140000
130000
120000
110000
100000
90000
80000
70000
60000
50000
50000
40000
30000
20000
10000
0
−10000
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)

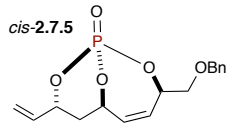

O
P
O
O
O
OBn
3000
2500
2000
1500
1000
500
0
130 110 90 70 50 30 10 −10 −30 −50 −70 −90 −110 −130 −150
f1 (ppm)

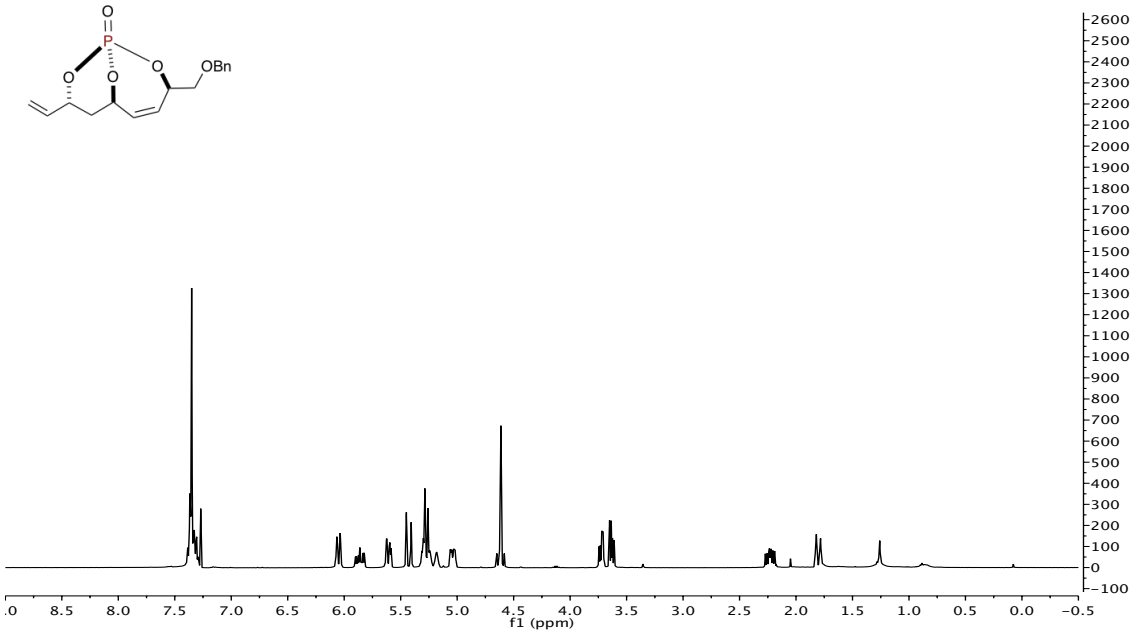
**(4*R*,6*R*)-2-(((*R*)-1-(benzyloxy)but-3-en-2-yl)oxy)-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide (2.7.3):**

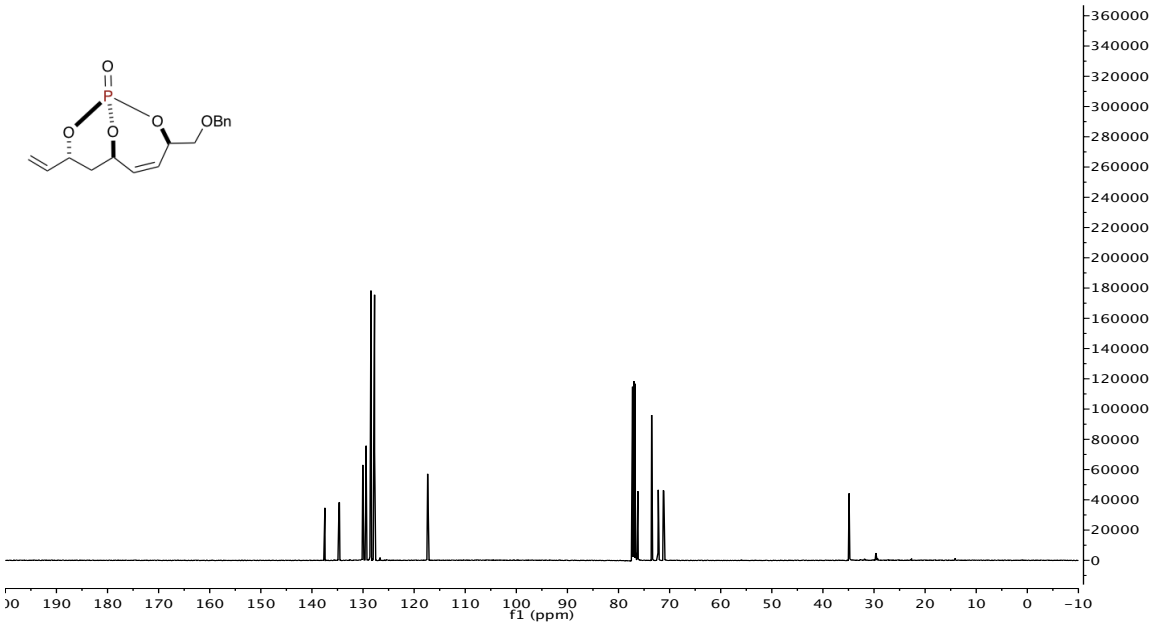


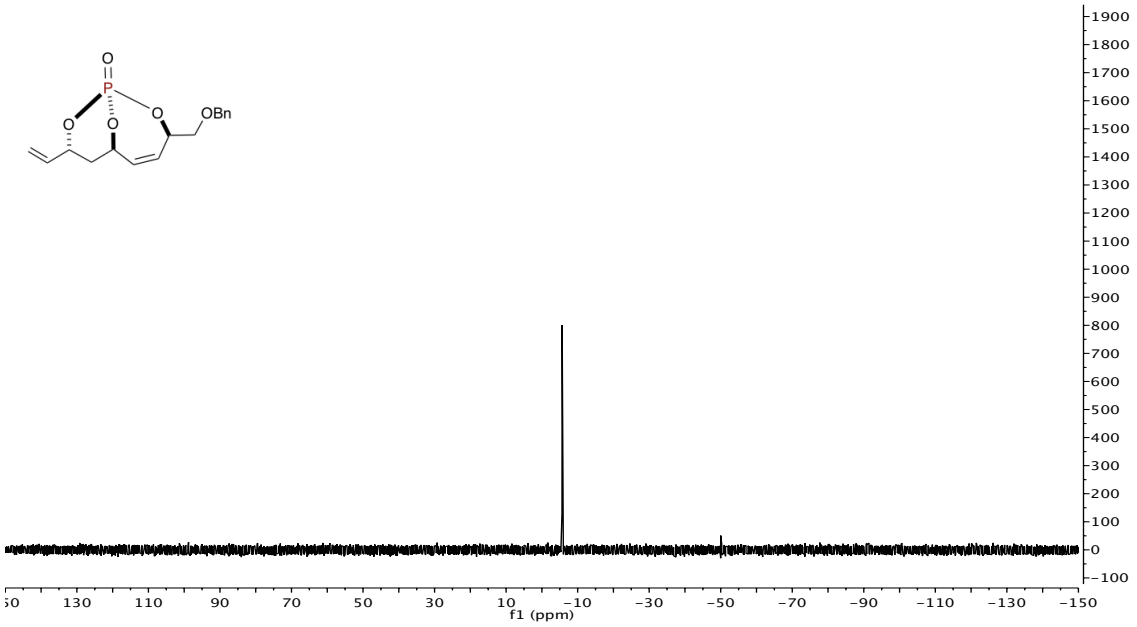



**(1*R*,3*R*,6*R*,8*R*)-3-((benzyloxy)methyl)-8-vinyl-2,9,10-trioxa-1-phosphabicyclo[4.3.1]-dec-4-ene 1-oxide (*cis*-2.7.5):**

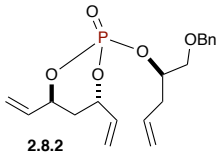


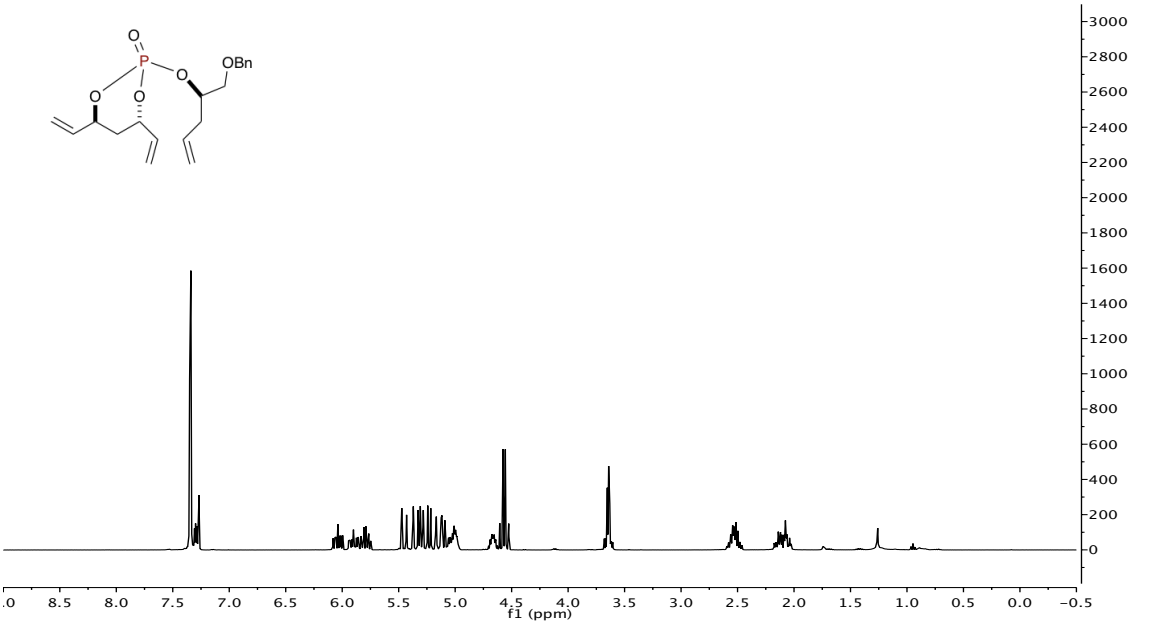

O
P
O
O
O
OBn
360000
340000
320000
300000
280000
260000
240000
220000
200000
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)

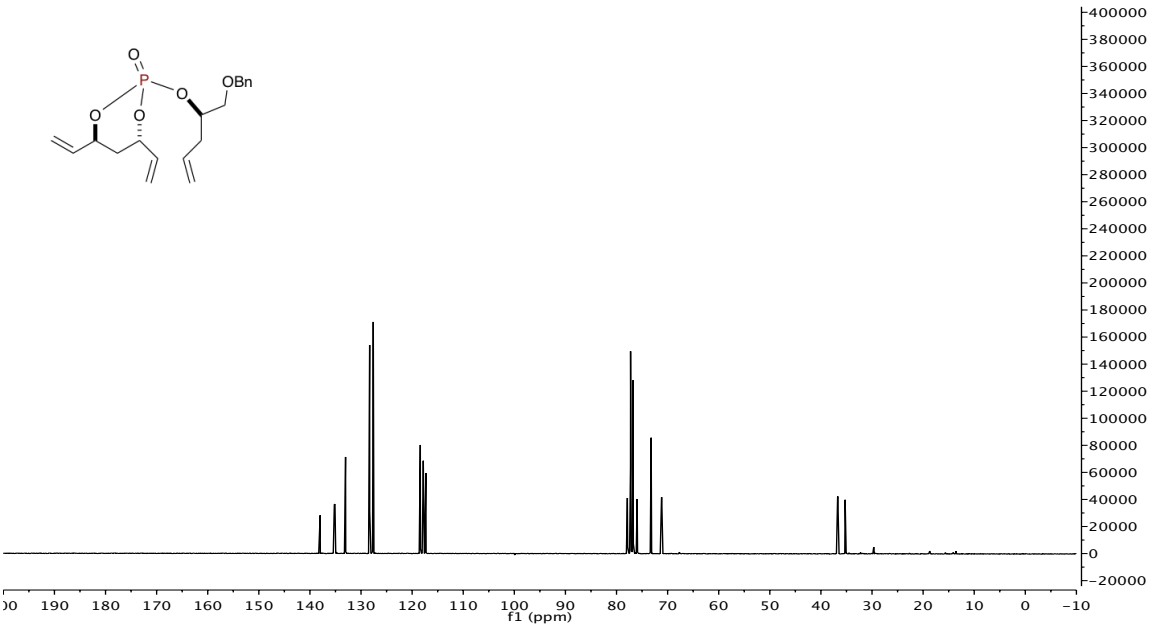

O
P
O
O
O
OBn
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−100
130 110 90 70 50 30 10 −10 −30 −50 −70 −90 −110 −130 −150
f1 (ppm)

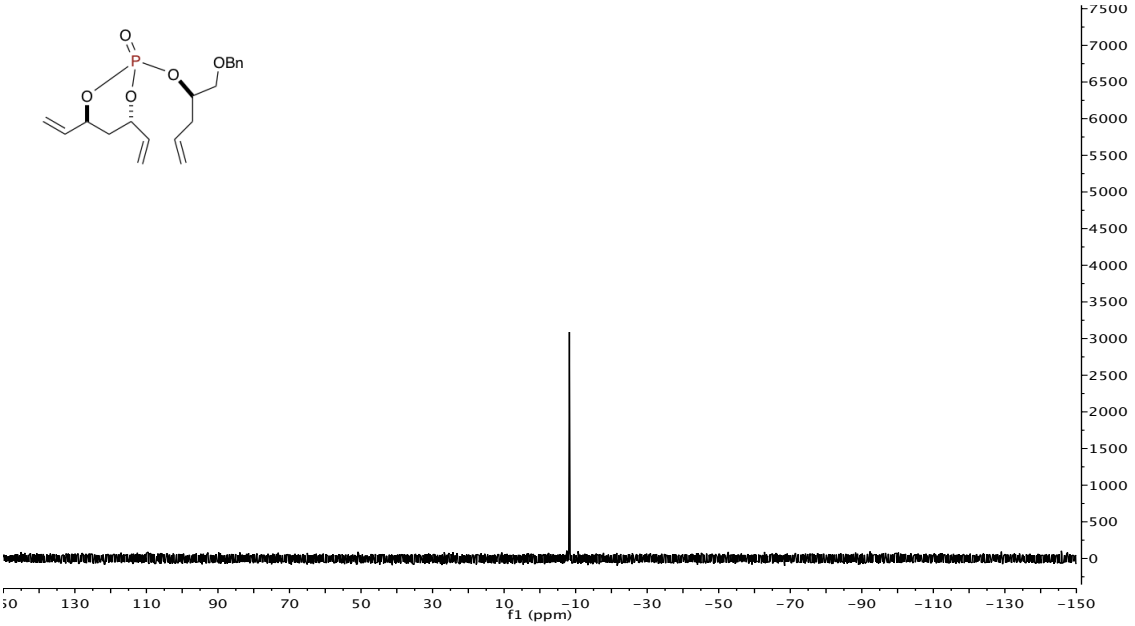
**(4*S*,6*S*)-2-(((*R*)-1-(benzyloxy)pent-4-en-2-yl)oxy)-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide (2.8.2):**



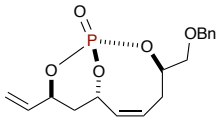

2.8.2



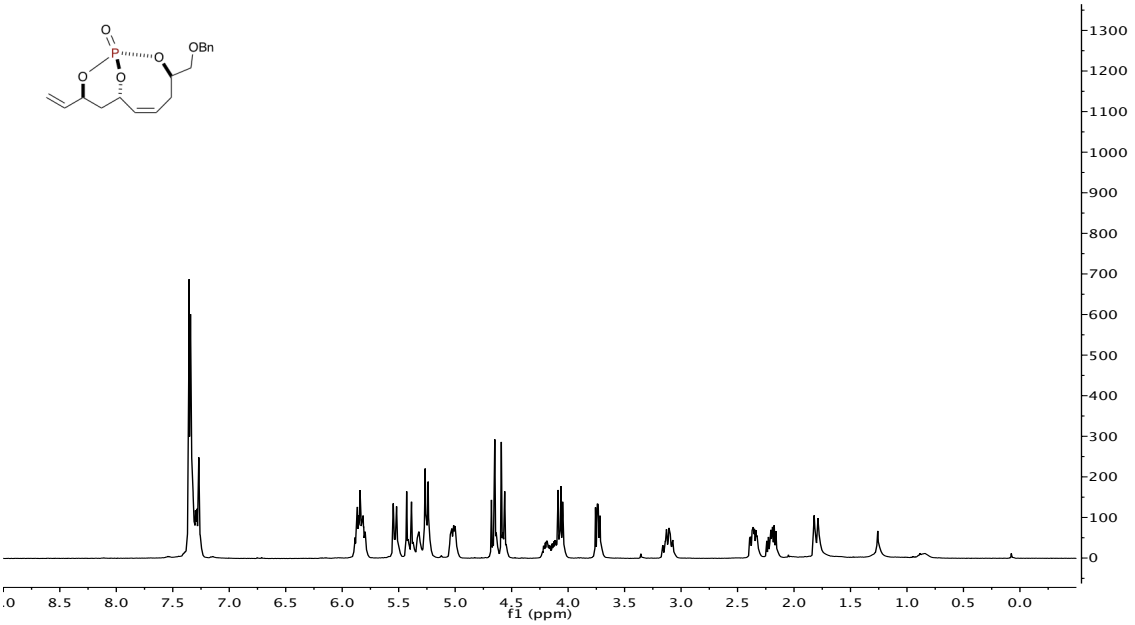



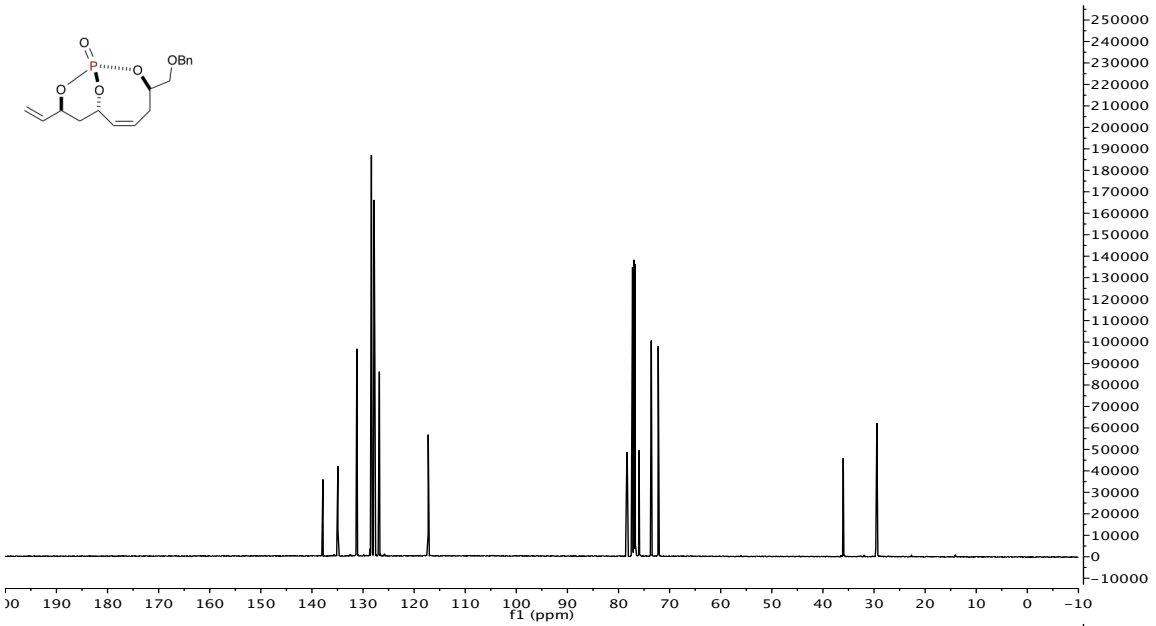


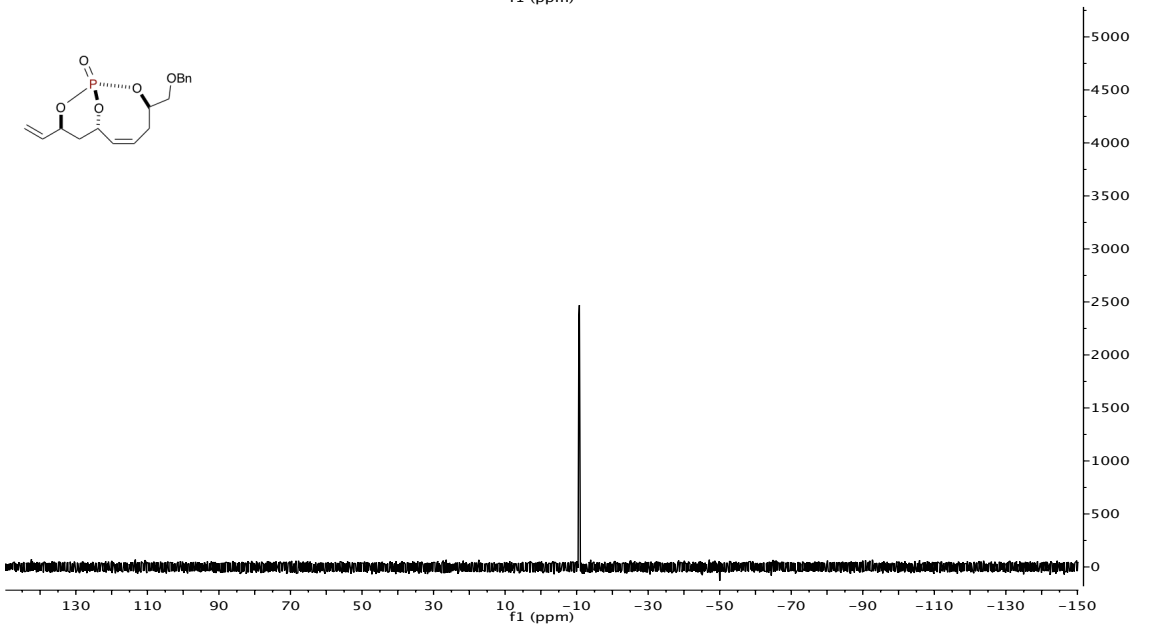

**(1*S*,3*R*,7*S*,9*S*,*Z*)-3-((benzyloxy)methyl)-9-vinyl-2,10,11-trioxa-1-phosphabicyclo[5.3.1]undec-5-ene 1-oxide (*trans*-2.8.4):**



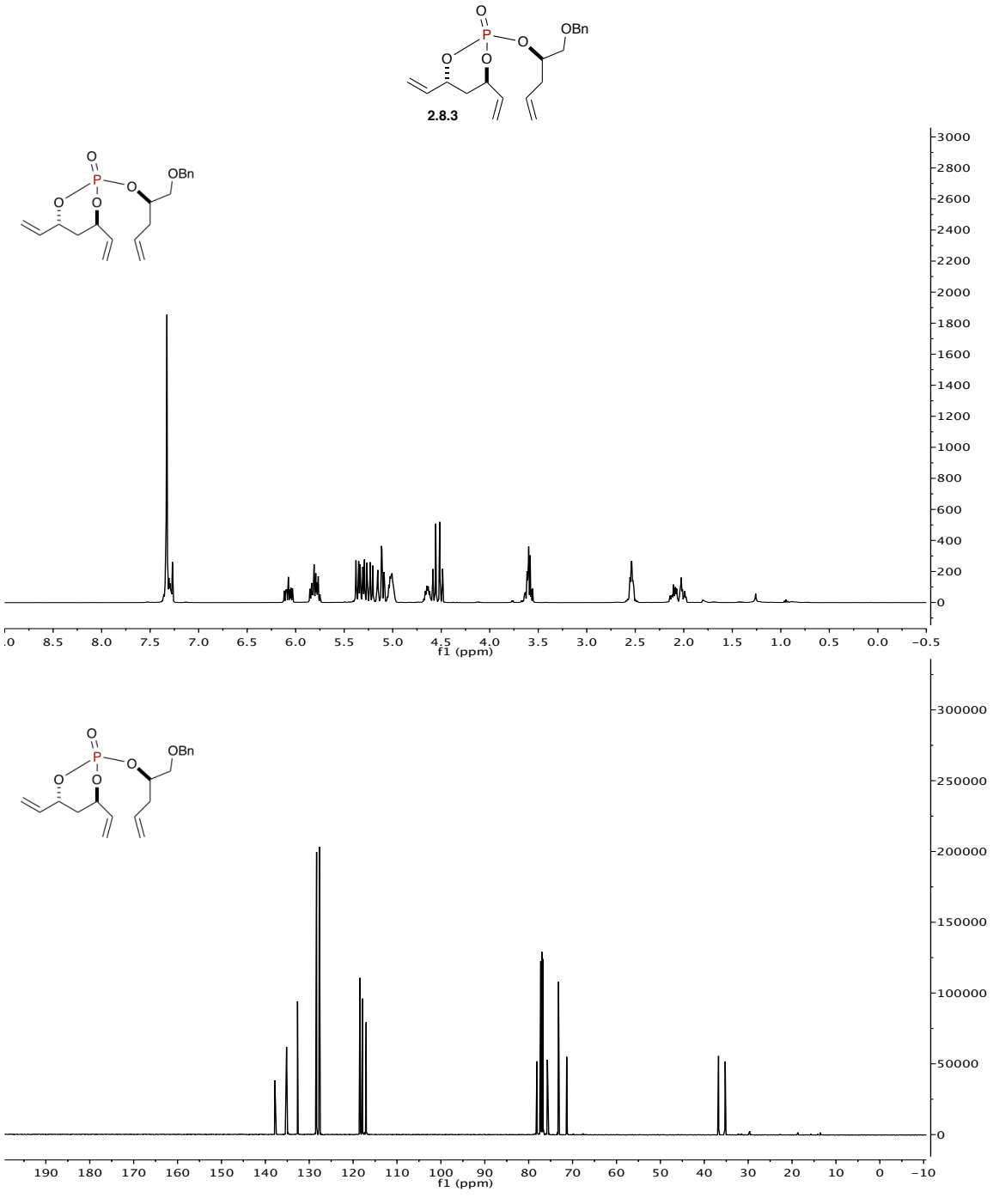

*trans*-**2.8.4**

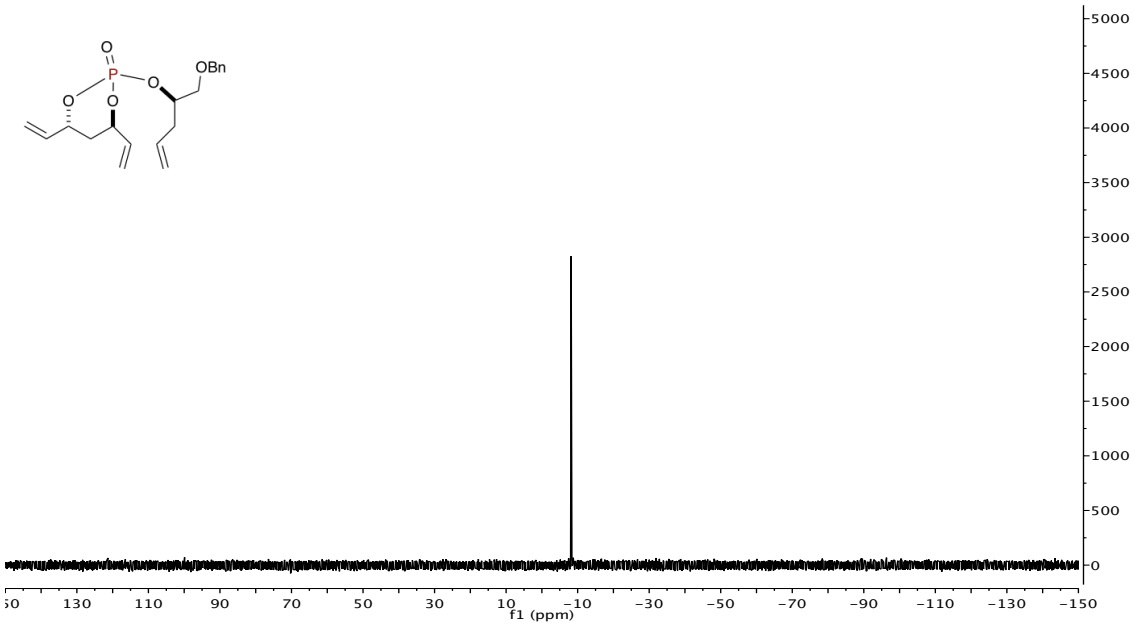



OBn
250000
240000
230000
220000
210000
200000
190000
180000
170000
160000
150000
140000
130000
120000
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
−10000
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)

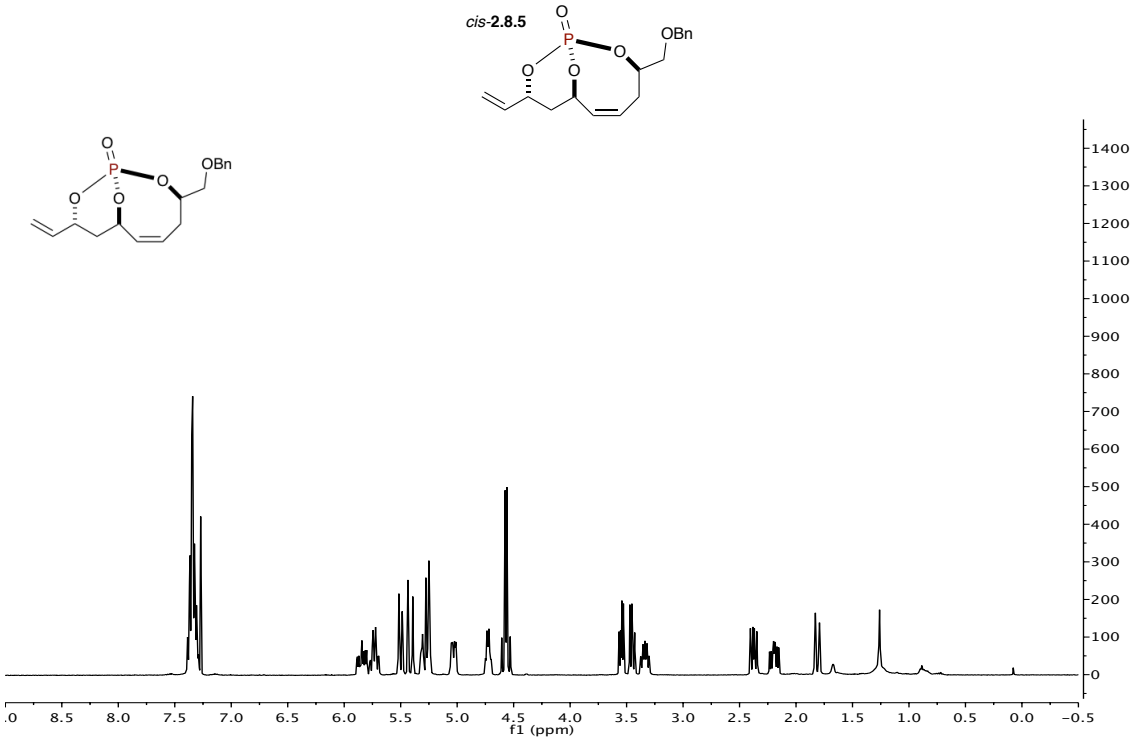

OBn
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
130 110 90 70 50 30 10 −10 −30 −50 −70 −90 −110 −130 −150
f1 (ppm)

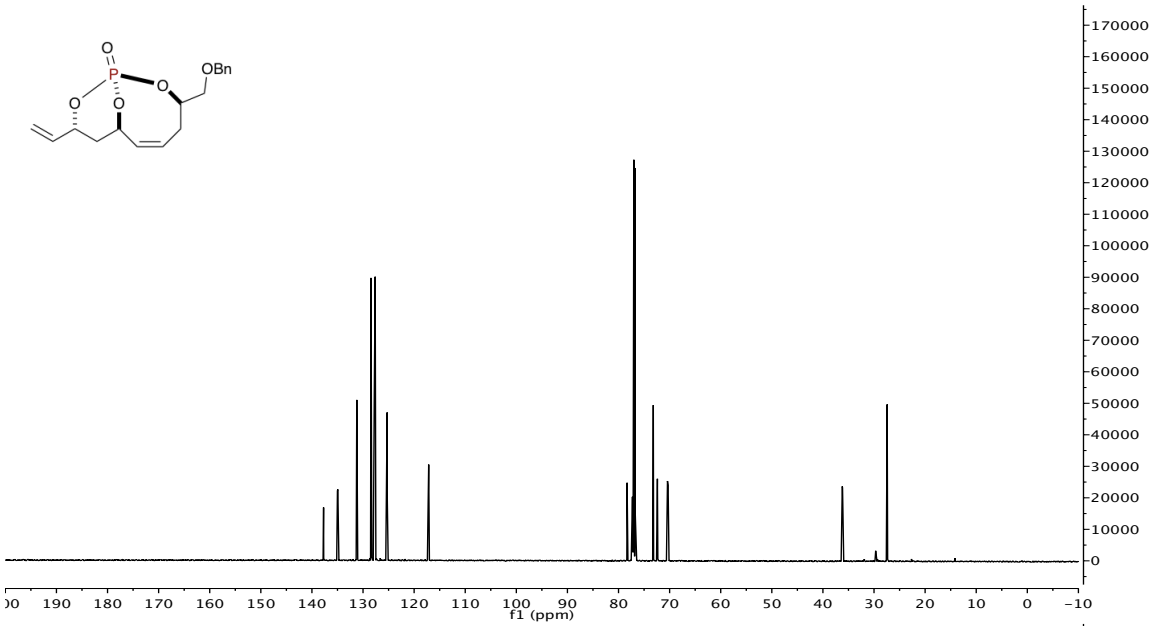
**(4*R*,6*R*)-2-(((*R*)-1-(benzyloxy)but-3-en-2-yl)oxy)-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide (2.8.3):**

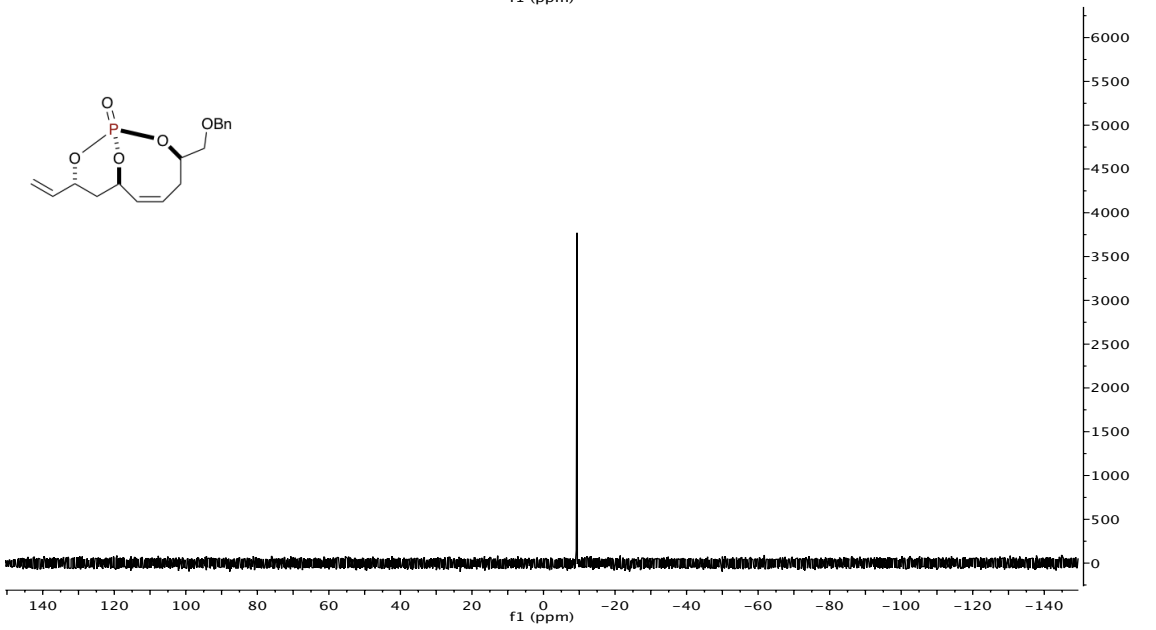




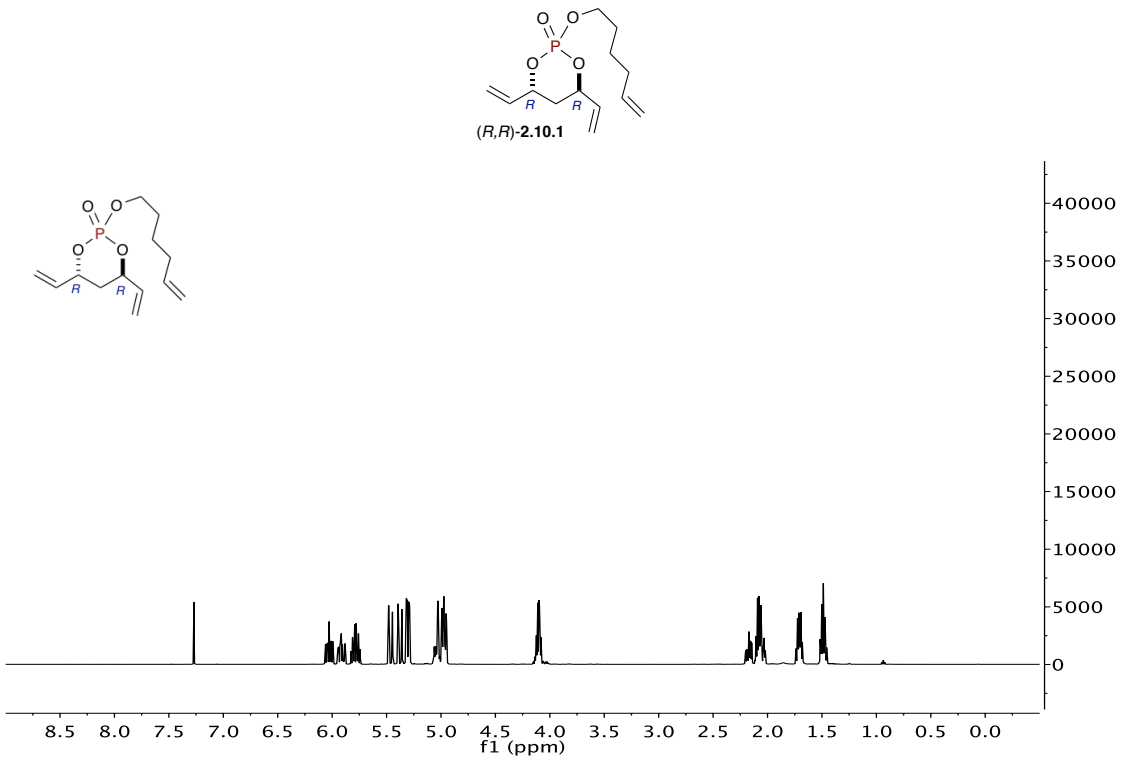

**(1*R*,3*R*,7*R*,9*R*,*Z*)-3-((benzyloxy)methyl)-9-vinyl-2,10,11-trioxa-1-phosphabicyclo-[5.3.1]undec-5-ene 1-oxide (*cis*-2.8.5):**

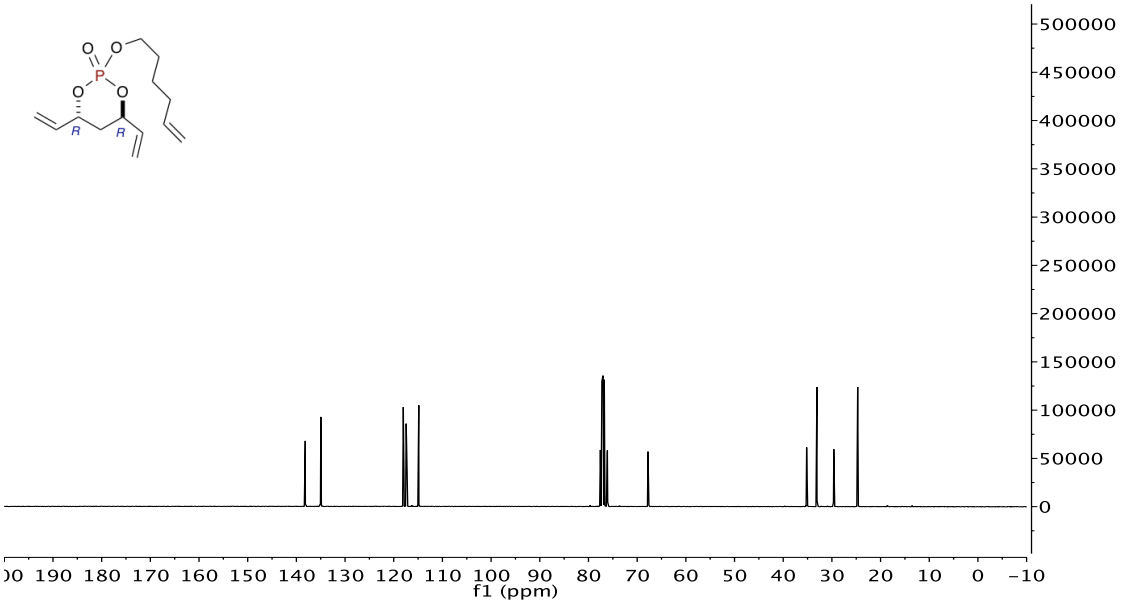


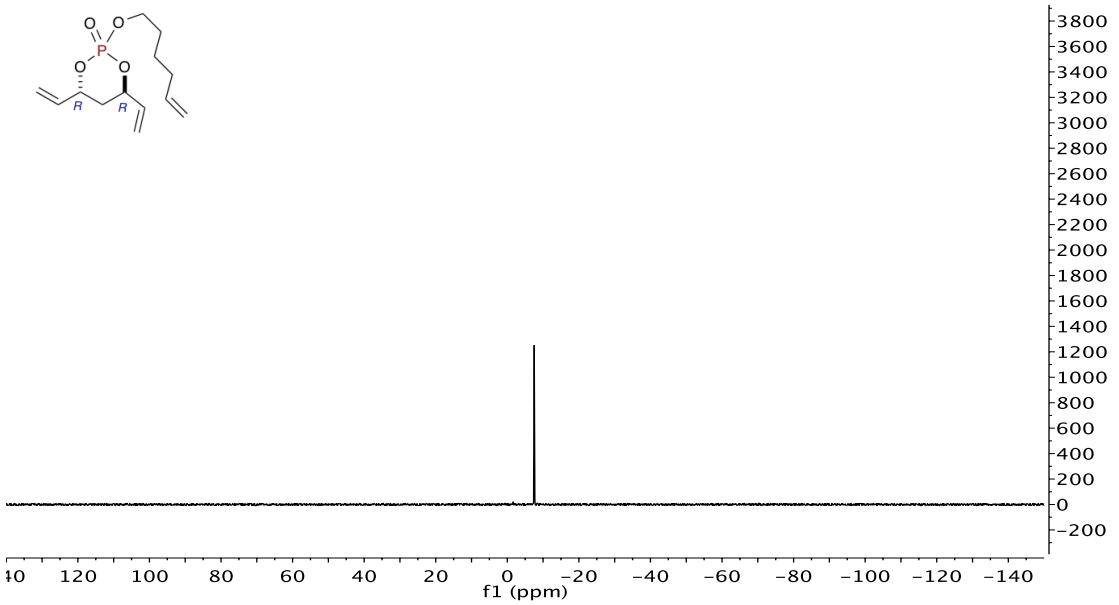

O
P
O
O
O
OBn
170000
160000
150000
140000
130000
120000
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)


O
P
O
O
O
OBn
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
140 120 100 80 60 40 20 0 −20 −40 −60 −80 −100 −120 −140
f1 (ppm)

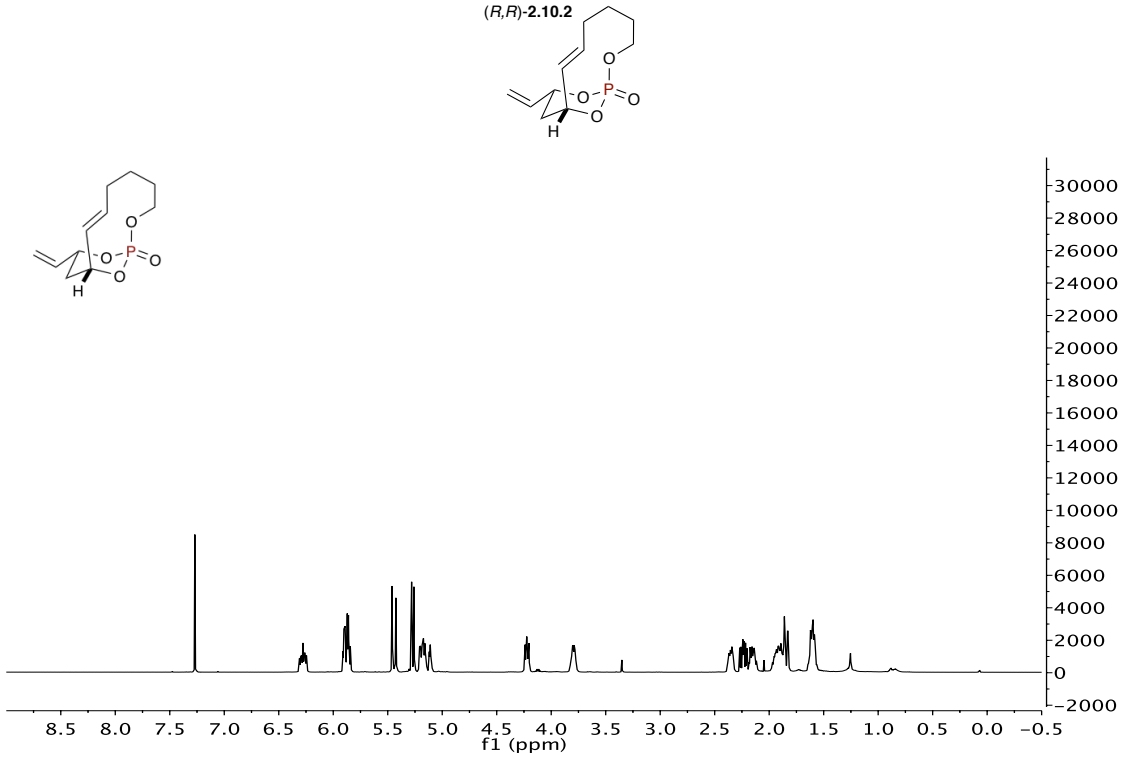
**(4*R*,6*R*)-2-(hex-5-en-1-yloxy)-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide (2.10.1):**

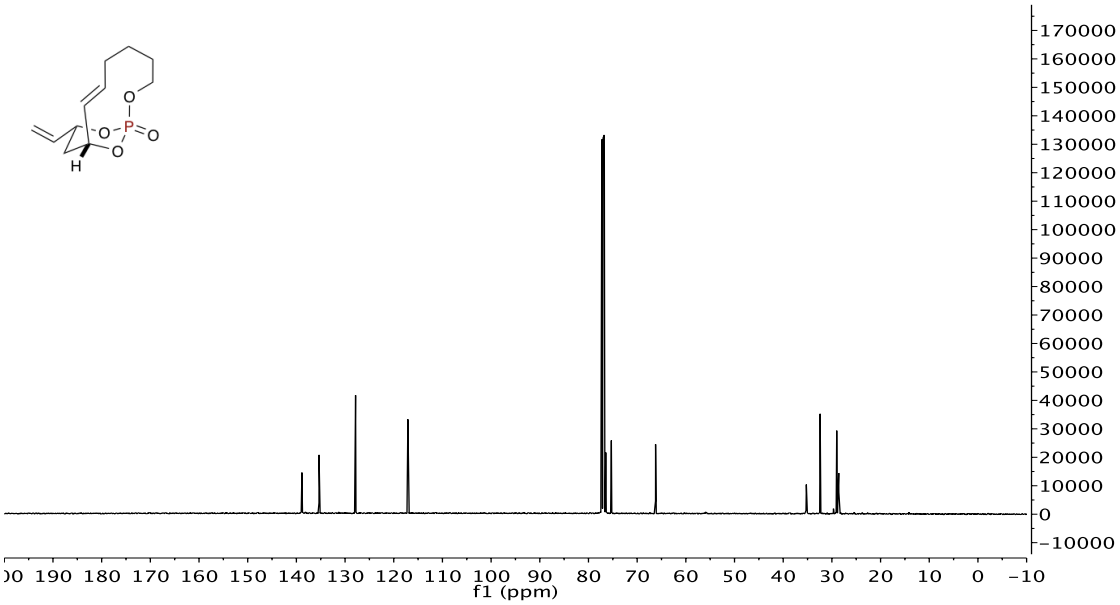


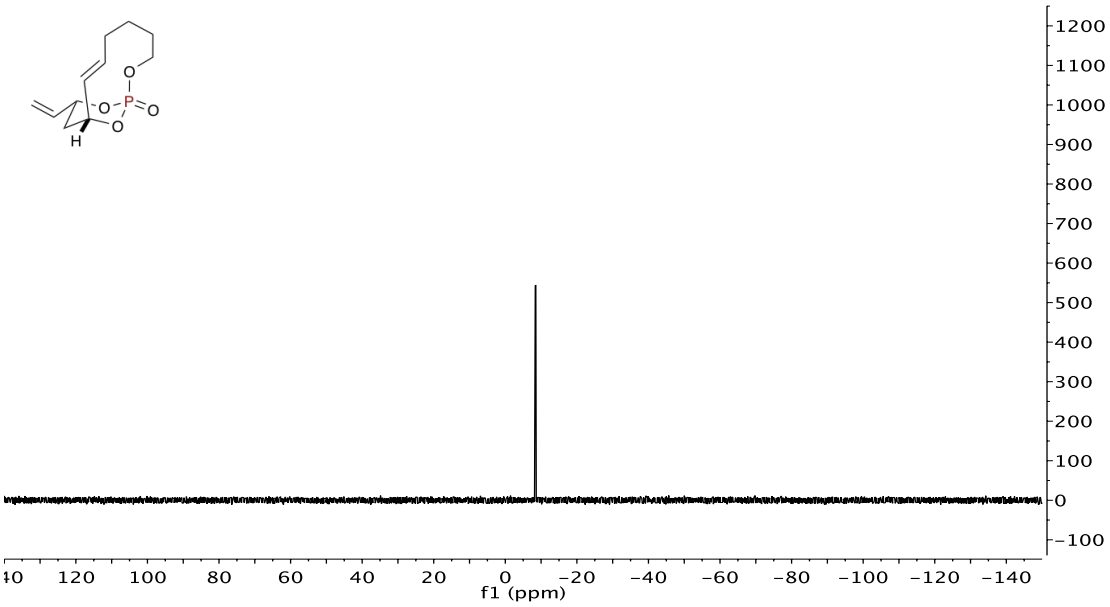





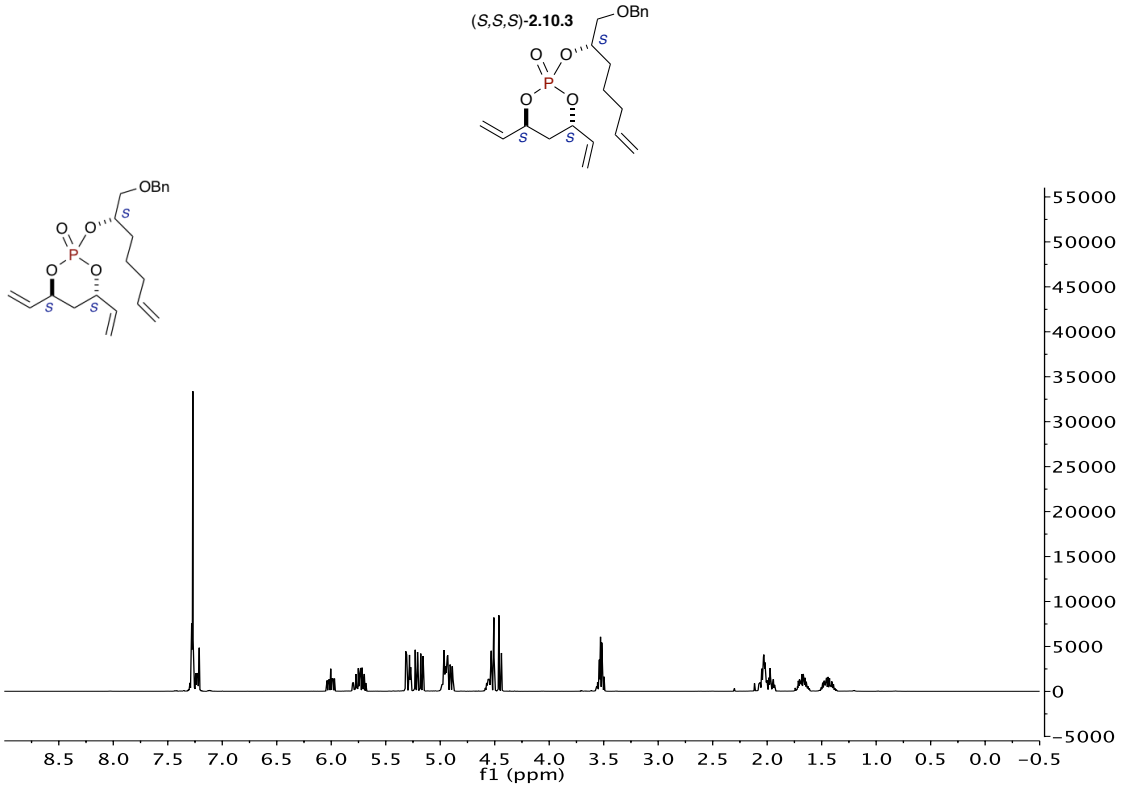

**(4*R*,6*R*)-2-(hex-5-en-1-yloxy)-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide (2.10.2):**

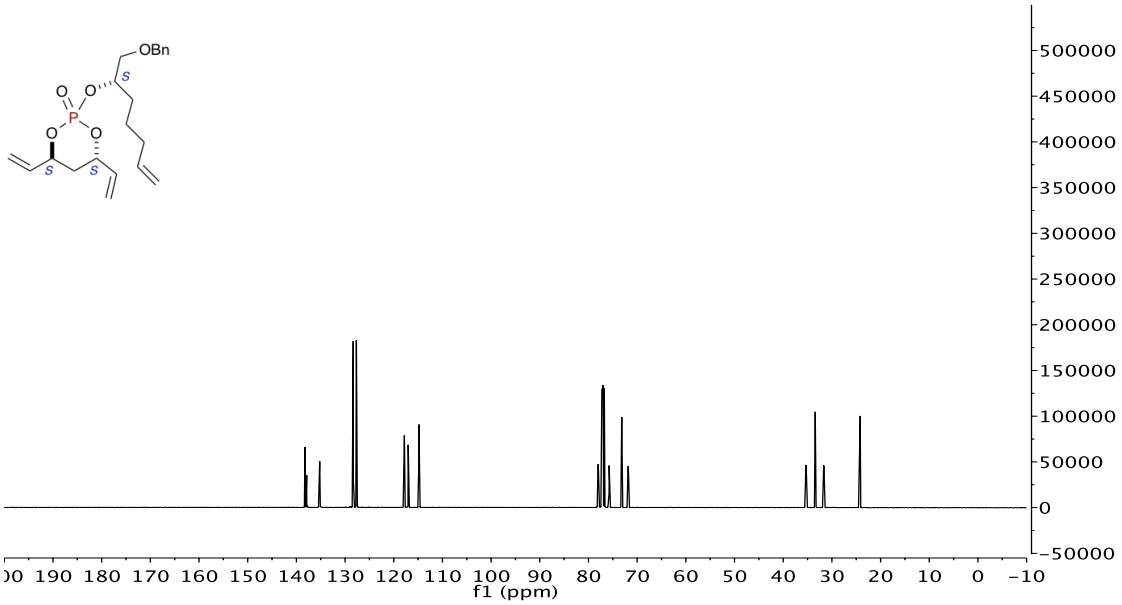


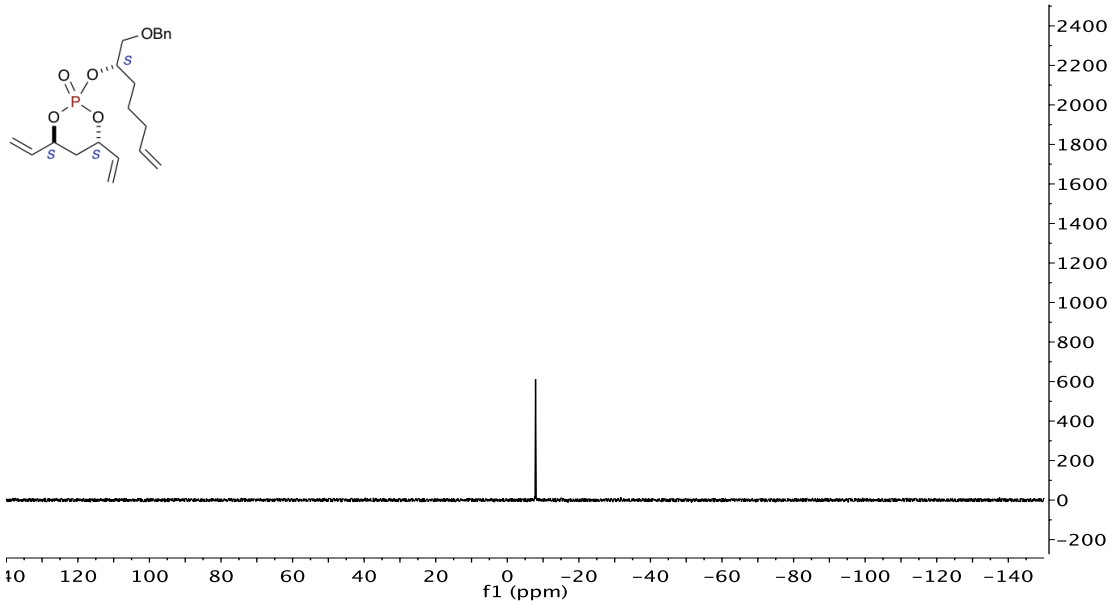

O
O
P
O
O
H
170000
160000
150000
140000
130000
120000
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
−10000
0 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)


O
O
P
O
O
H
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−100
40 120 100 80 60 40 20 0 −20 −40 −60 −80 −100 −120 −140
f1 (ppm)

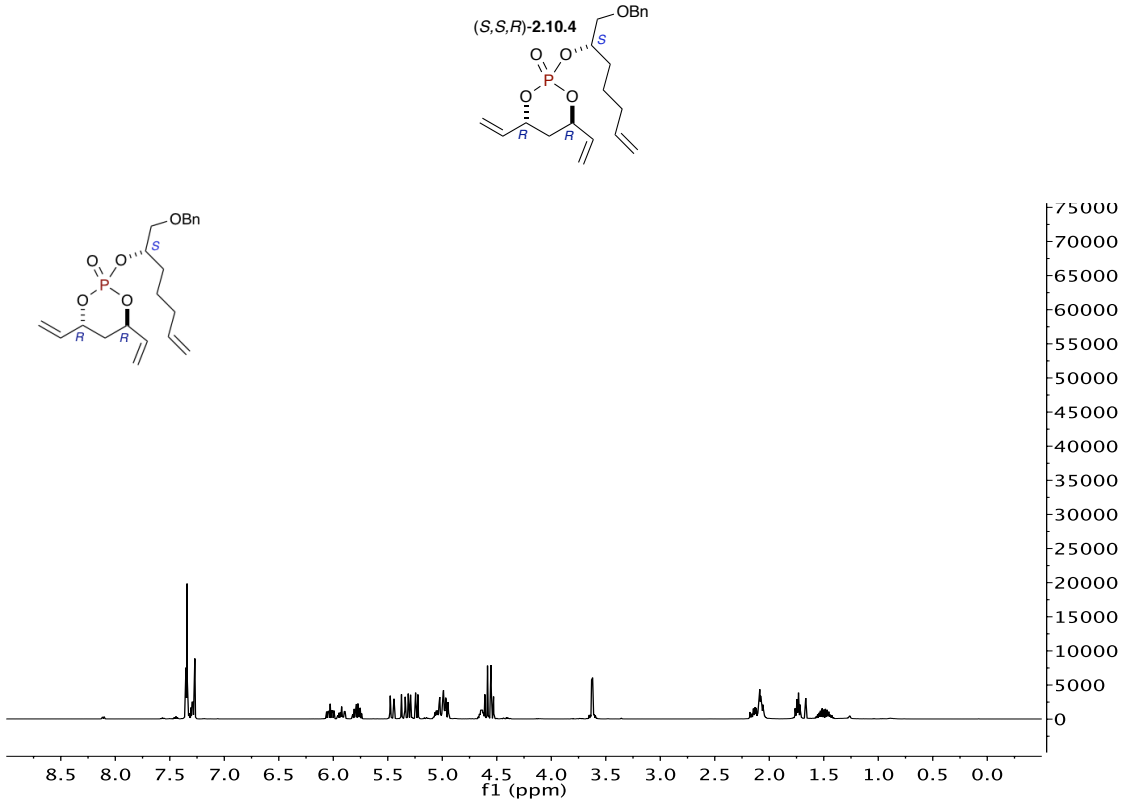
**(4*S*,6*S*)-2-(((*S*)-1-(benzyloxy)hept-6-en-2-yl)oxy)-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide (2.10.3):**

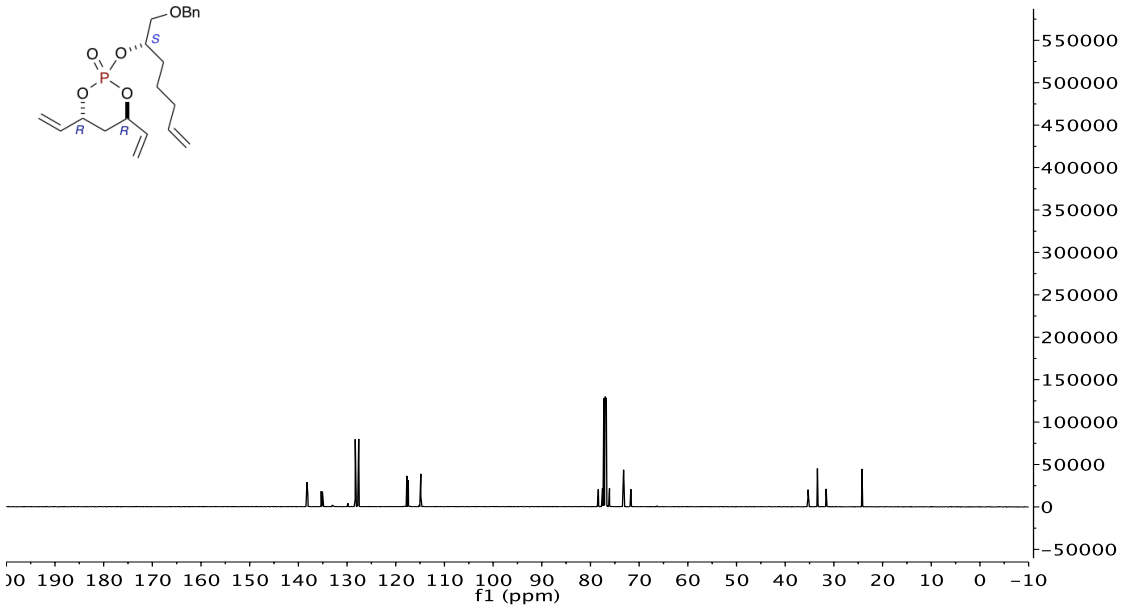


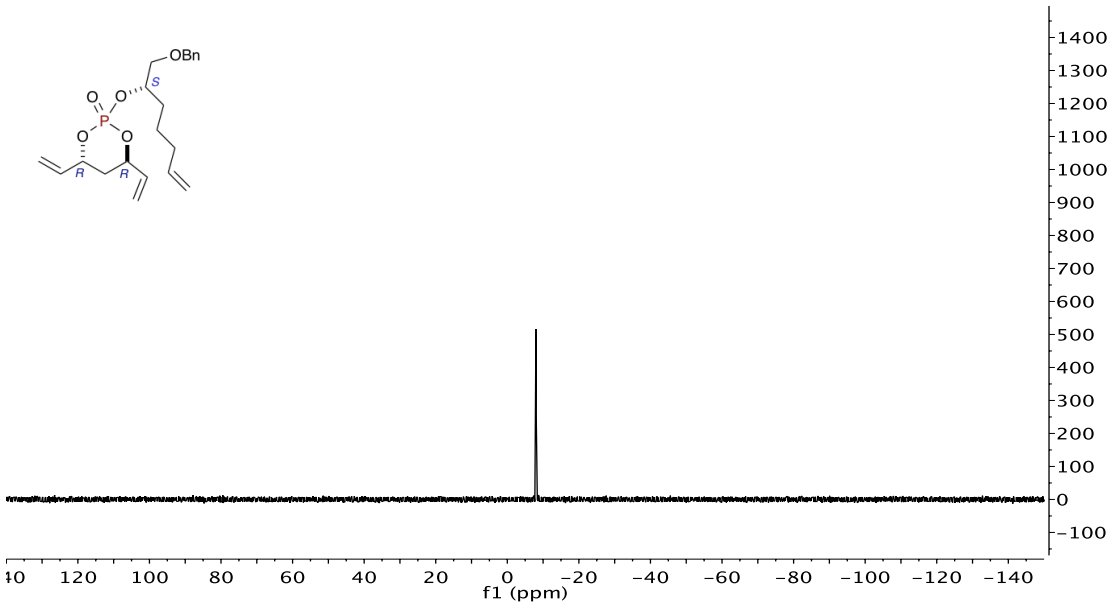





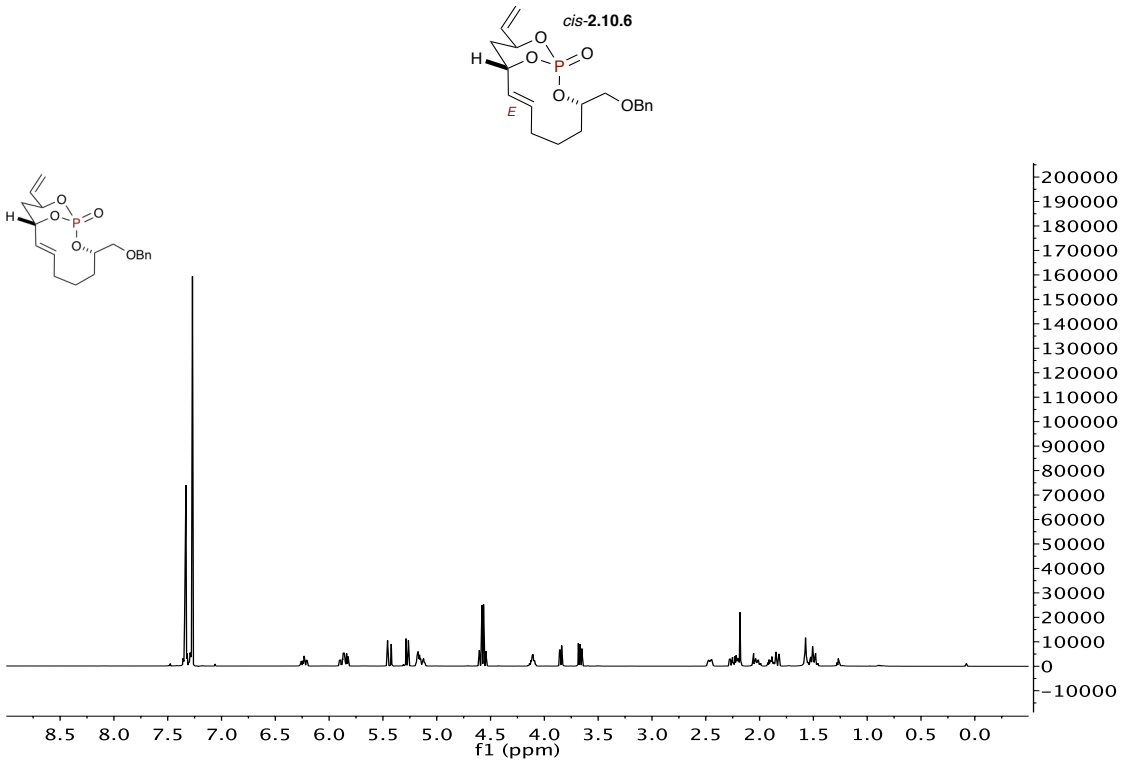

**(4*R*,6*R*)-2-(((*S*)-1-(benzyloxy)hept-6-en-2-yl)oxy)-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide (2.10.4):**

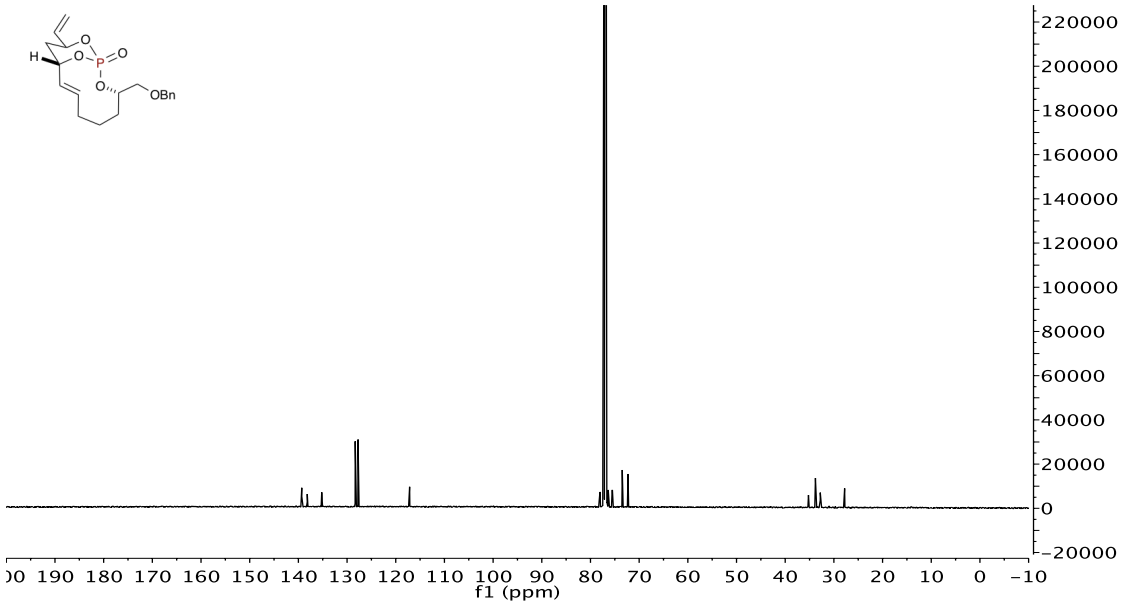


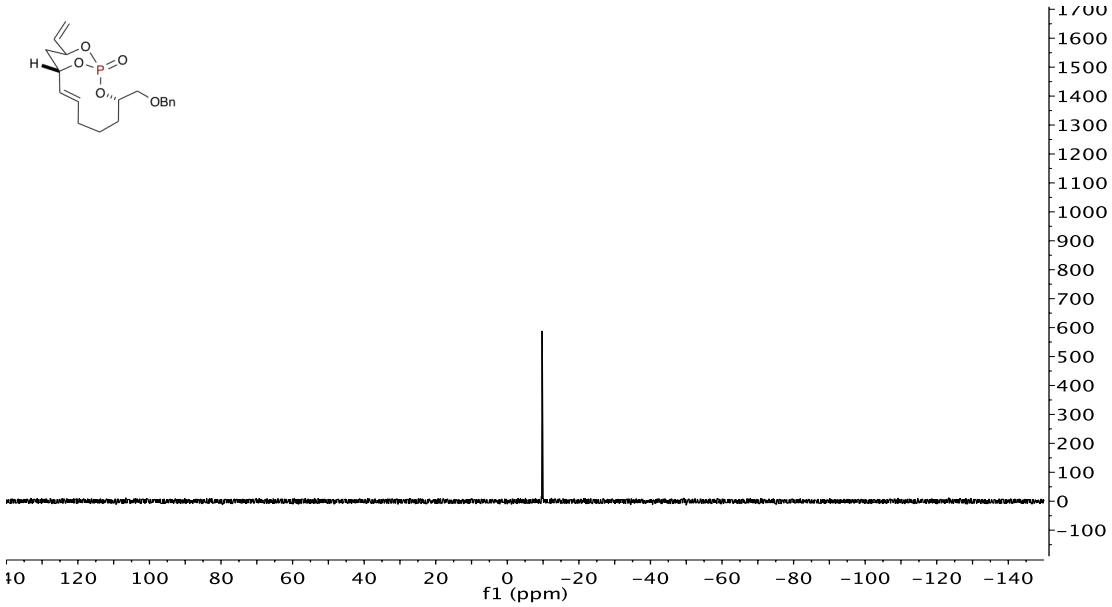

OBn
S
O
O
P
O
O
R
R
550000
500000
450000
400000
350000
300000
250000
200000
150000
100000
50000
0
−50000
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)


OBn
S
O
O
P
O
O
R
R
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−100
120 100 80 60 40 20 0 −20 −40 −60 −80 −100 −120 −140
f1 (ppm)

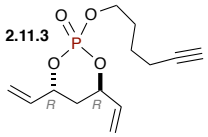
**(1*S*,3*S*,9*S*,11*S*,*E*)-3-((benzyloxy)methyl)-11-vinyl-2,12,13-trioxa-1-phosphabicyclo[7.3.1]tridec-7-ene 1-oxide (2.10.6):**

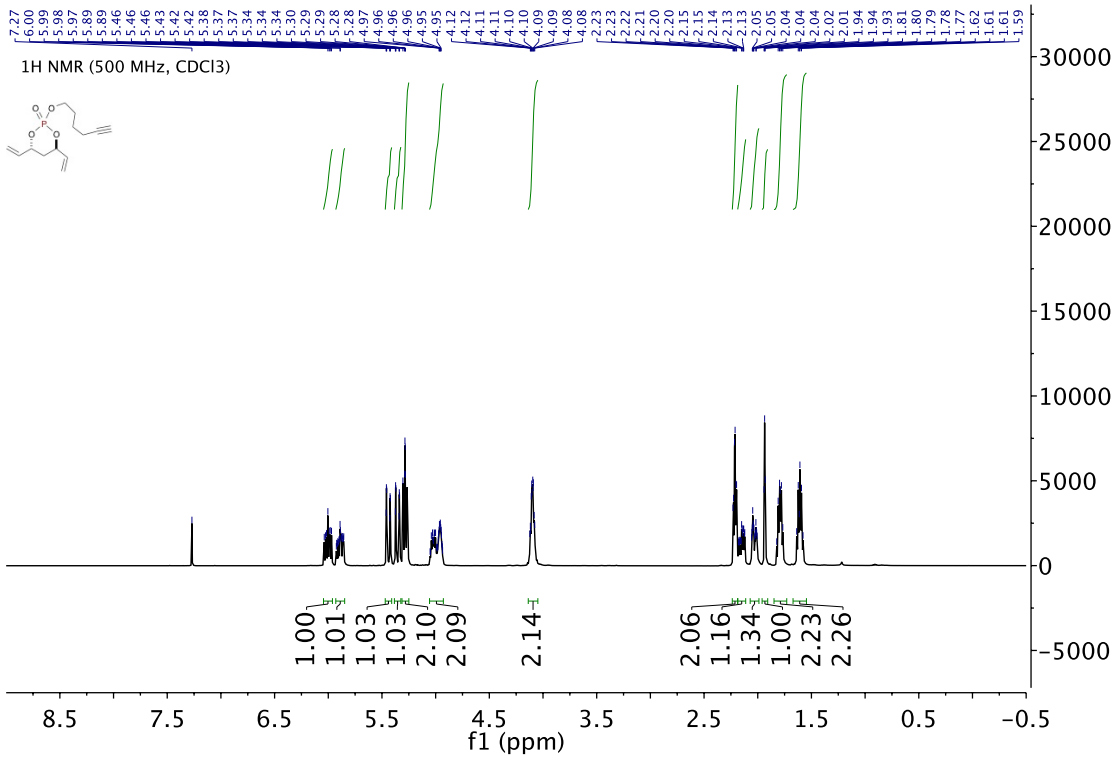


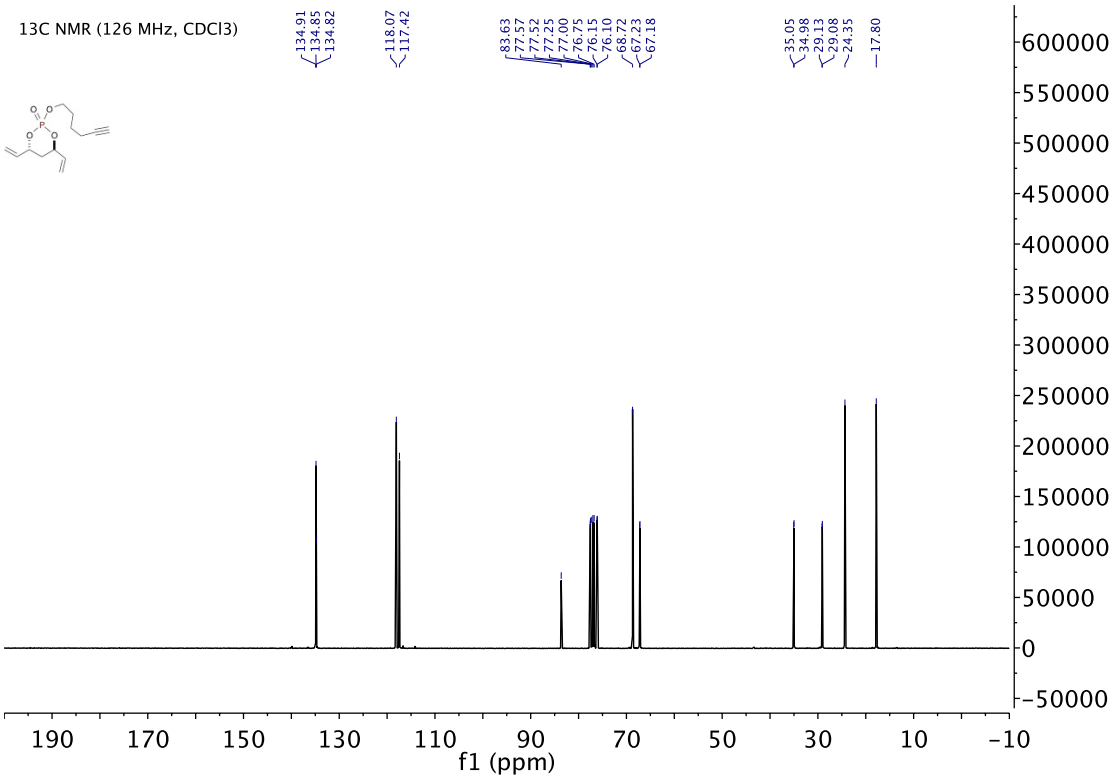



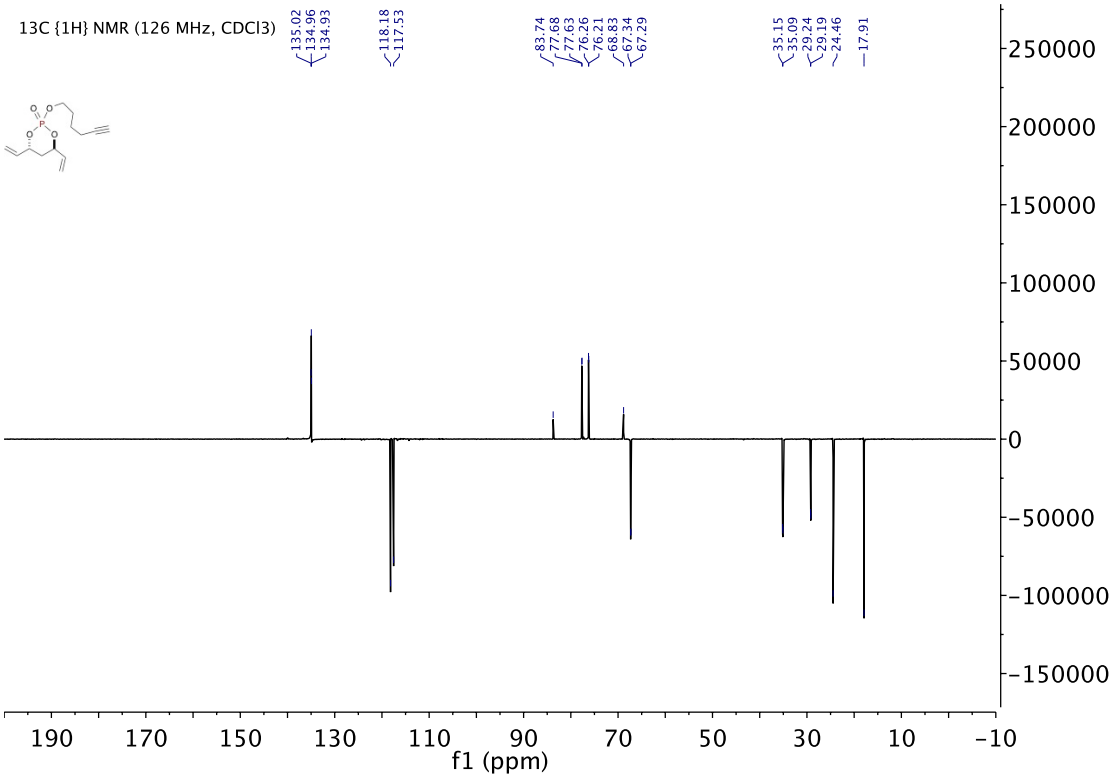


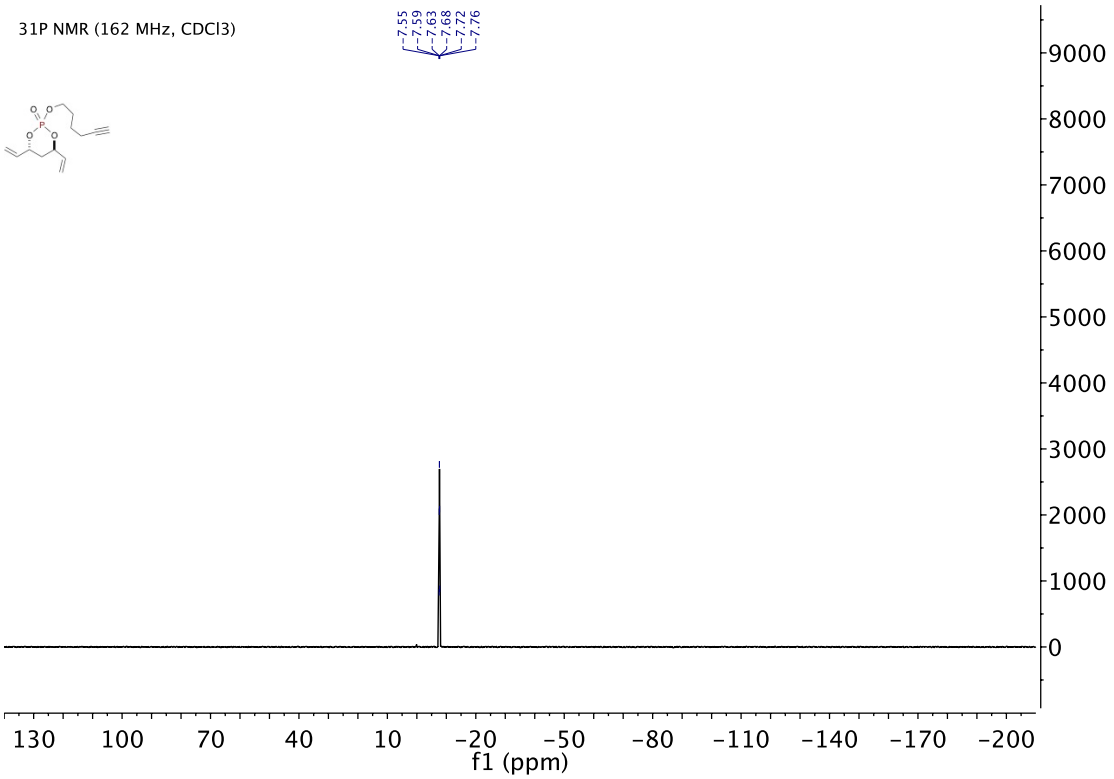

**(4*R*,6*R*)-2-(hex-5-yn-1-yloxy)-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide (2.11.3)**

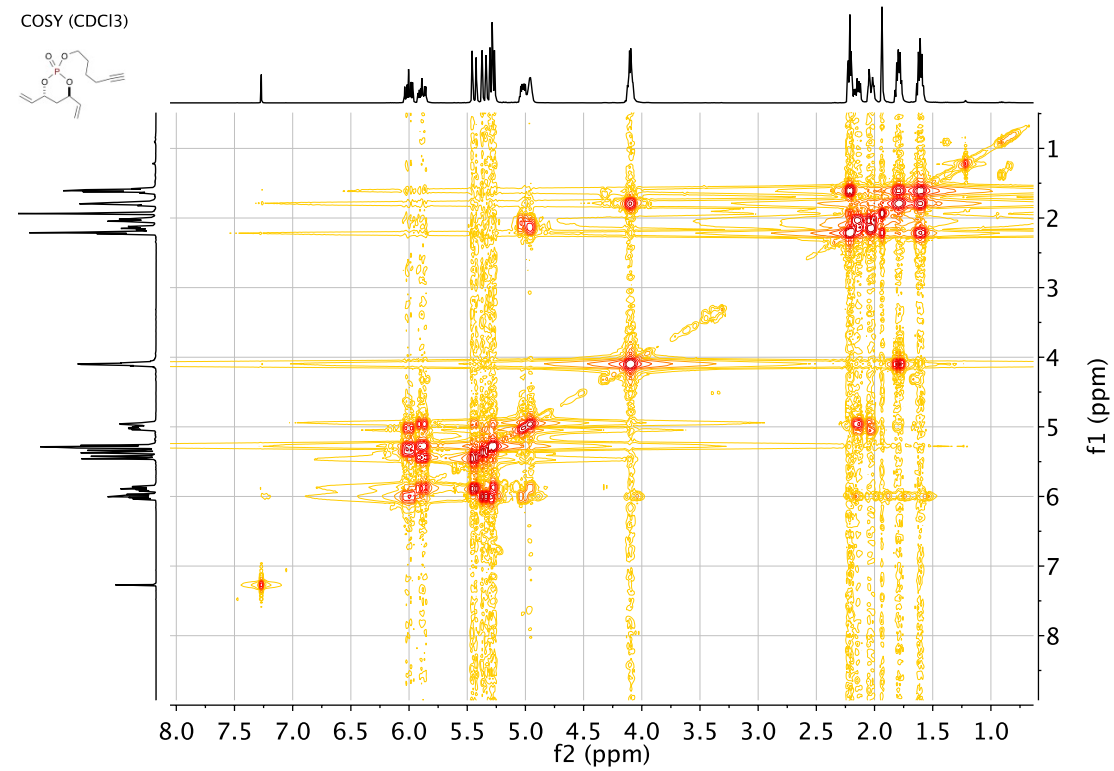


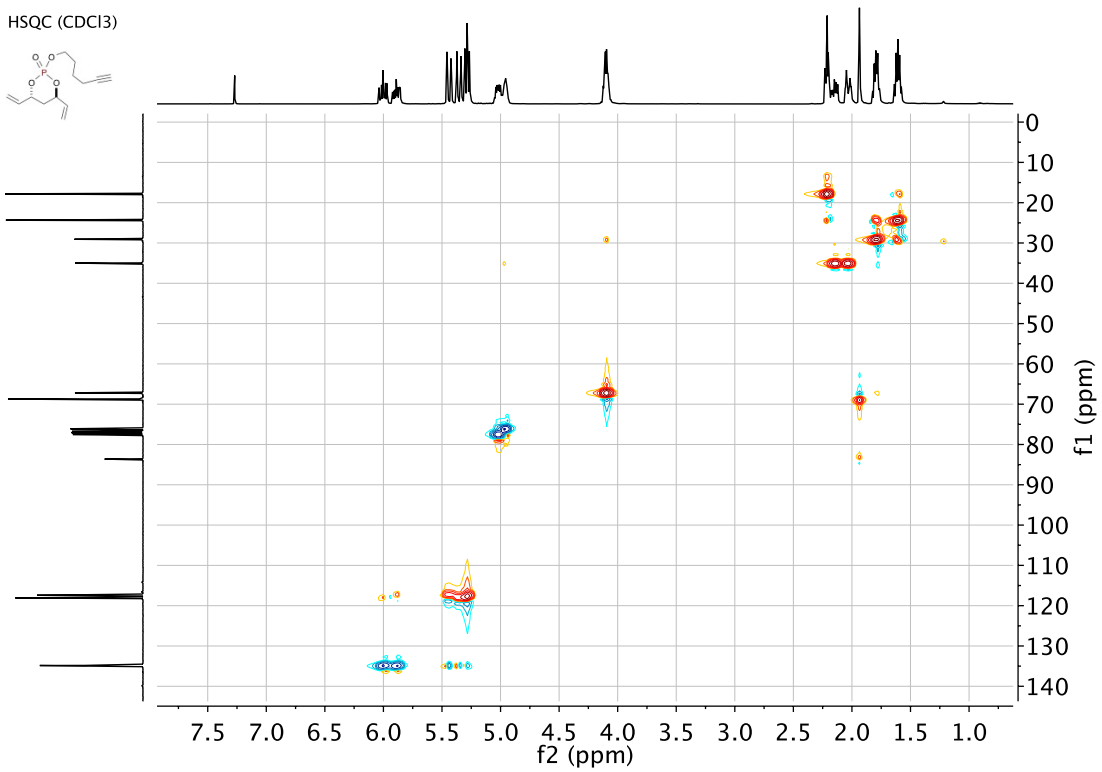




13C NMR (126 MHz, CDCl3)
134.91
134.85
134.82
118.07
117.42
83.63
77.57
77.52
77.25
77.00
76.75
76.15
76.10
68.72
67.23
67.18
35.05
34.98
29.13
29.08
24.35
17.80
600000
550000
500000
450000
400000
350000
300000
250000
200000
150000
100000
50000
0
-50000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

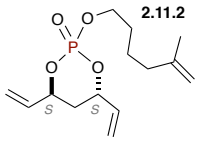

13C {1H} NMR (126 MHz, CDCl3)
135.02
134.96
134.93
118.18
117.53
83.74
77.68
77.63
76.26
76.21
68.83
67.34
67.29
35.15
35.09
29.24
29.19
24.46
17.91
250000
200000
150000
100000
50000
0
-50000
-100000
-150000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

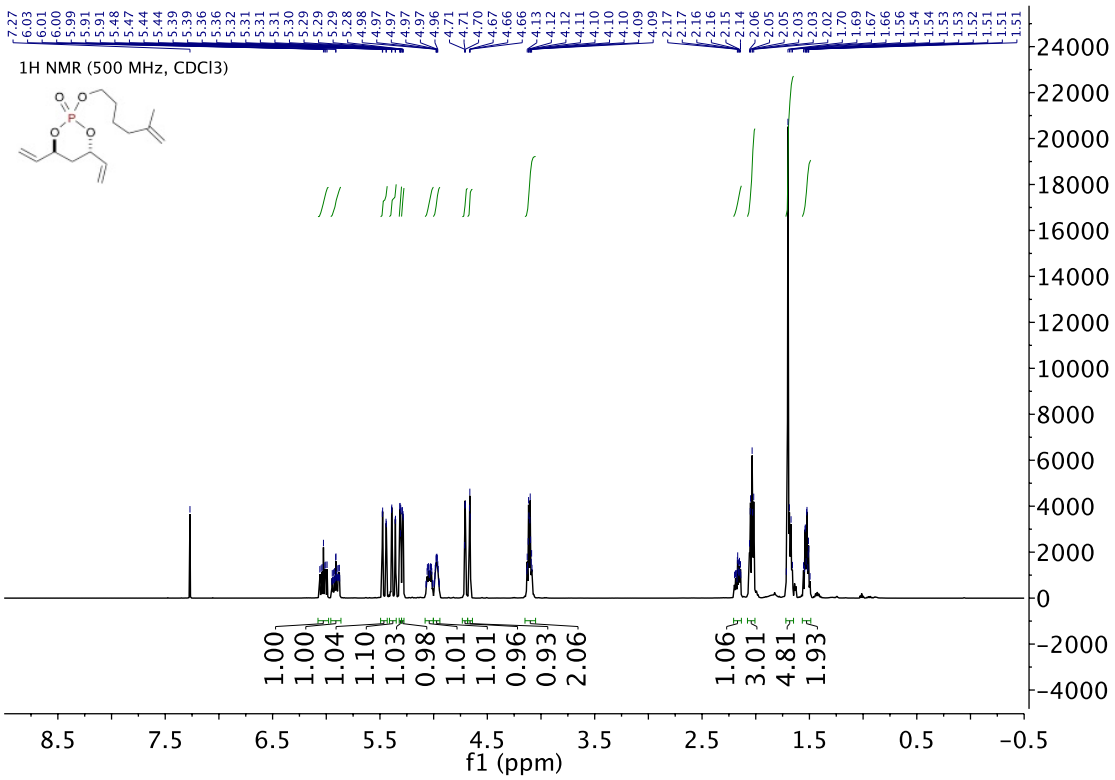

31P NMR (162 MHz, CDCl3)
7.55
7.59
7.63
7.68
7.72
7.76
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
130
100
70
40
10
-20
-50
-80
-110
-140
-170
-200
f1 (ppm)

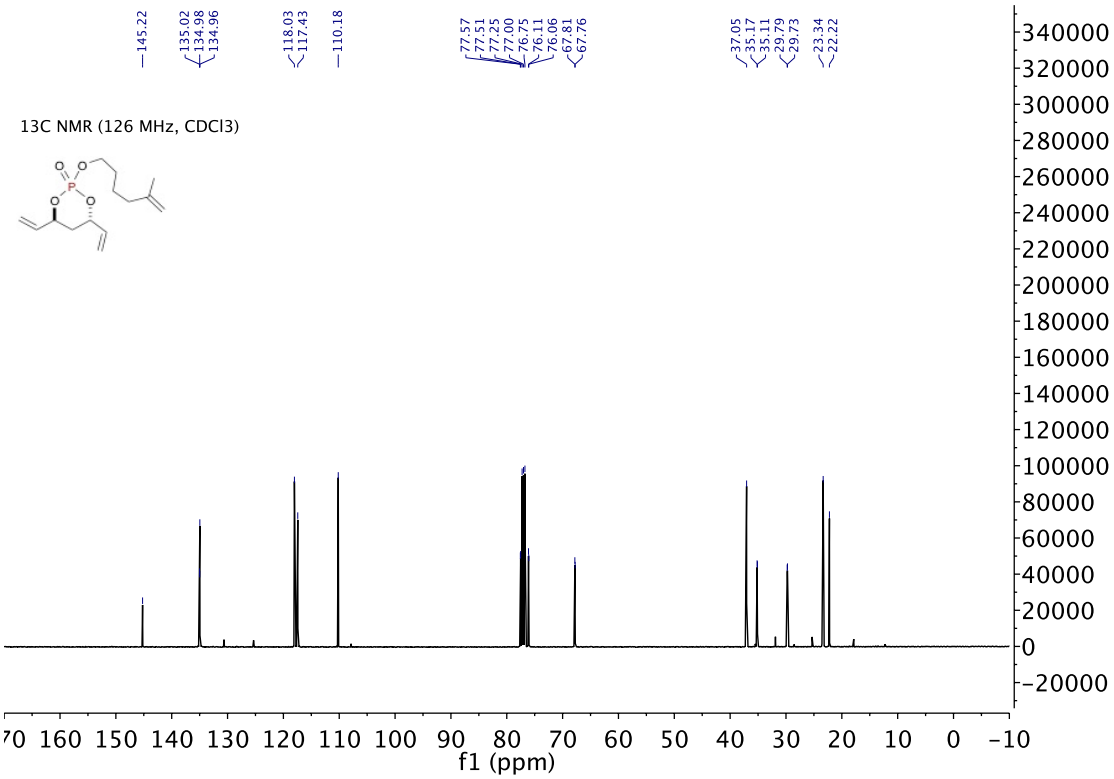

COSY (CDCl3)
1
2
3
4
5
6
7
8
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)

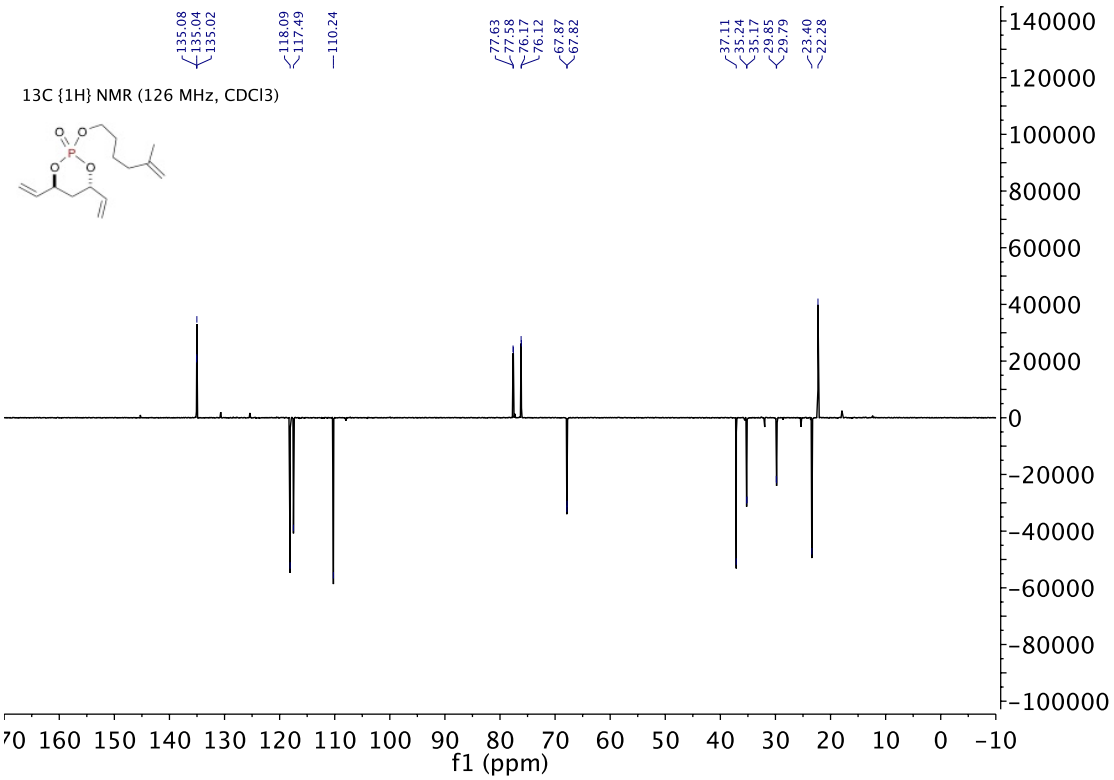

HSQC (CDCl3)
f2 (ppm)
f1 (ppm)
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140

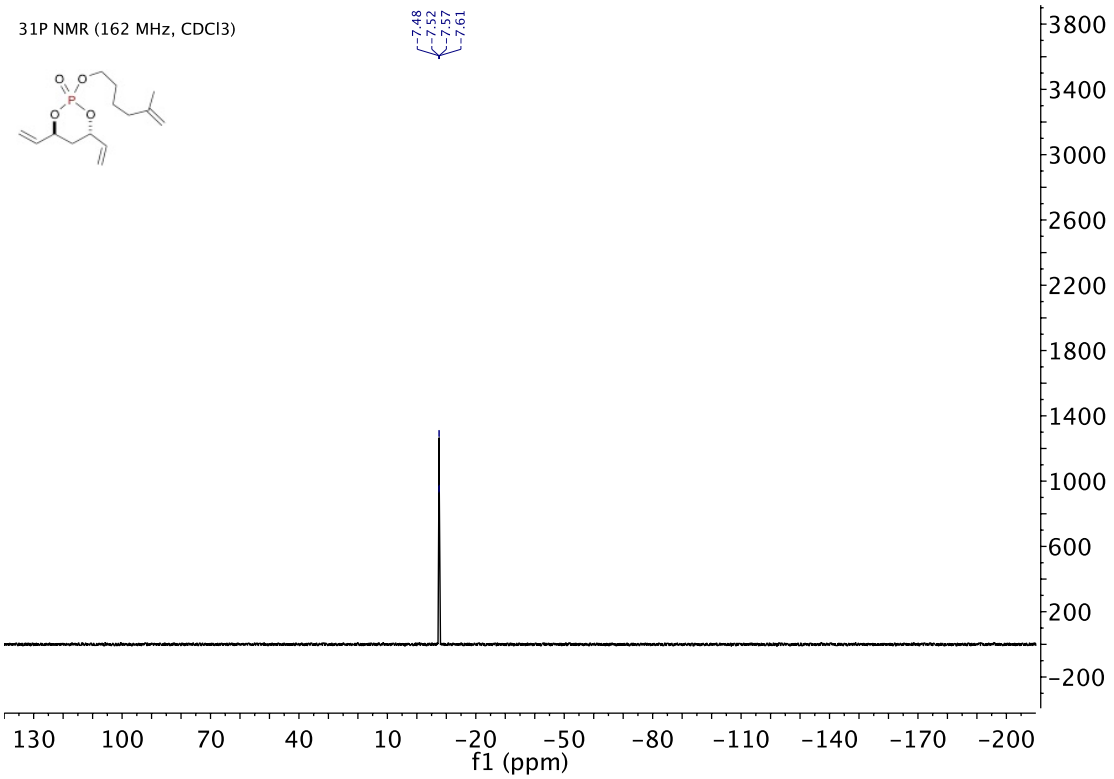
**(4*S*,6*S*)-2-((5-methylhex-5-en-1-yl)oxy)-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide (2.11.2)**

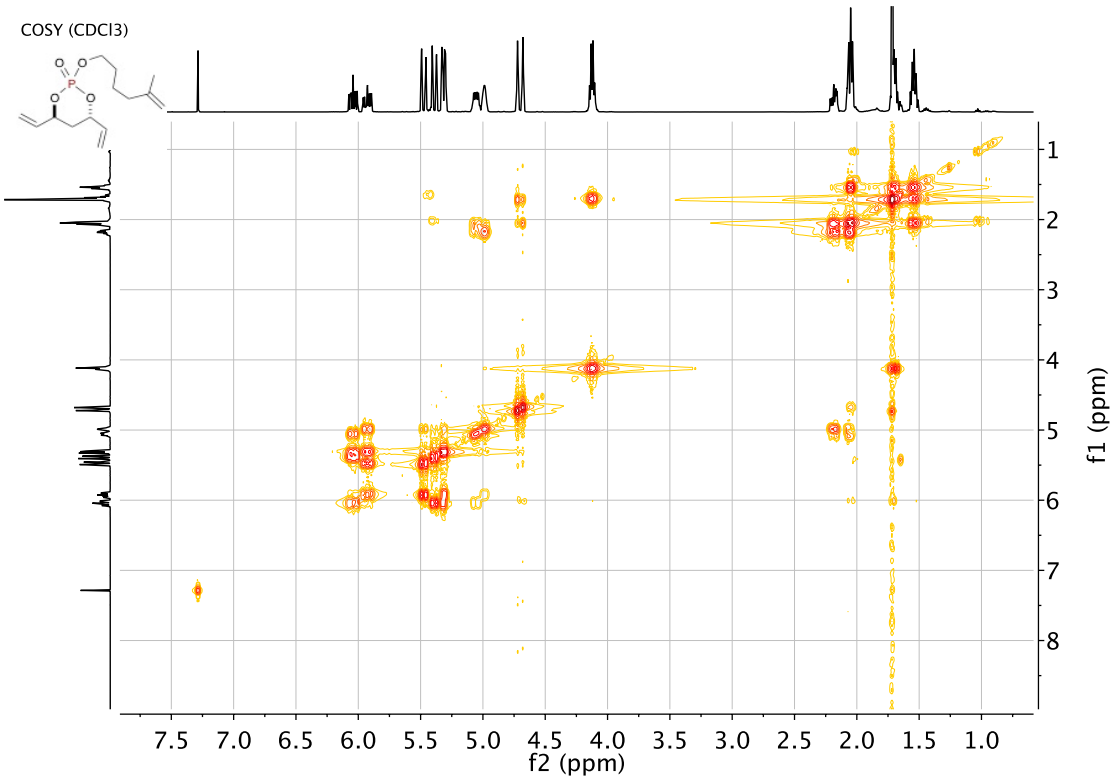


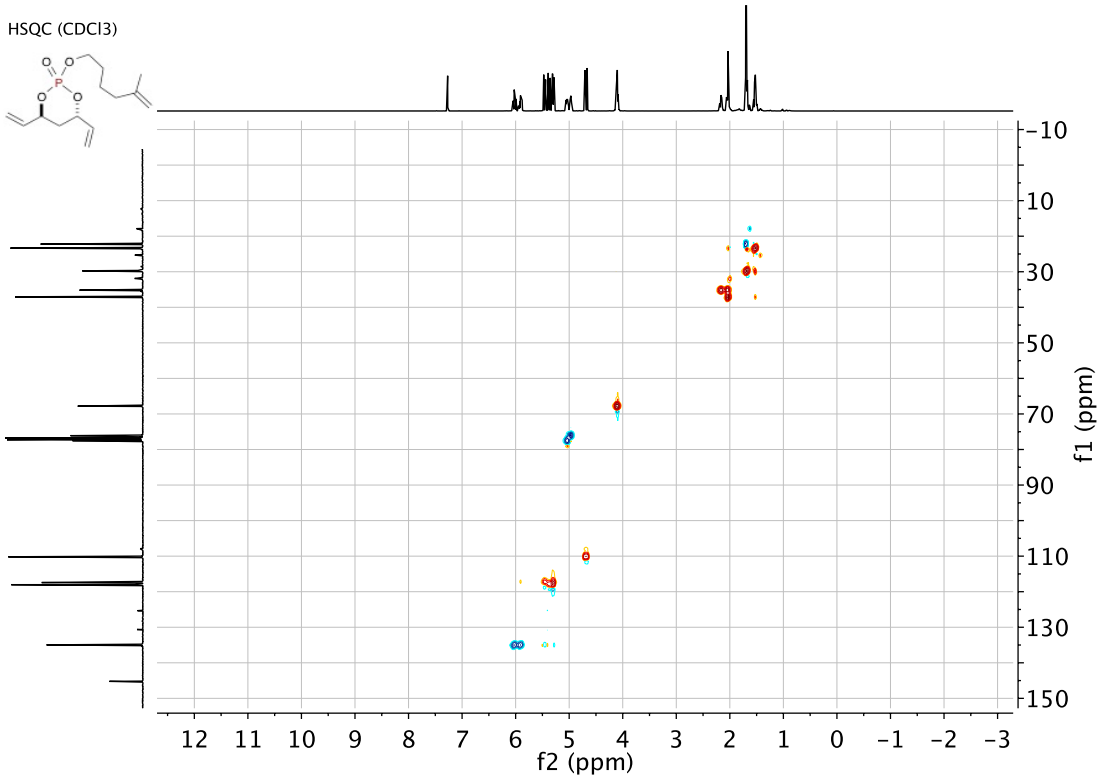




145.22
135.02
134.98
134.96
118.03
117.43
110.18
77.57
77.51
77.25
77.00
76.75
76.11
76.06
67.81
67.76
37.05
35.17
35.11
29.79
29.73
23.34
22.22
13C NMR (126 MHz, CDCl3)
f1 (ppm)

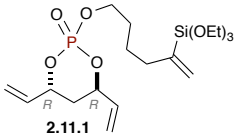

135.08
135.04
135.02
118.09
117.49
110.24
77.63
77.58
76.17
76.12
67.87
67.82
37.11
35.24
35.17
29.85
29.79
23.40
22.28
13C {1H} NMR (126 MHz, CDCl3)
f1 (ppm)


31P NMR (162 MHz, CDCl3)
7.48
7.52
7.57
7.61
3800
3400
3000
2600
2200
1800
1400
1000
600
200
-200
130
100
70
40
10
-20
-50
-80
-110
-140
-170
-200
f1 (ppm)

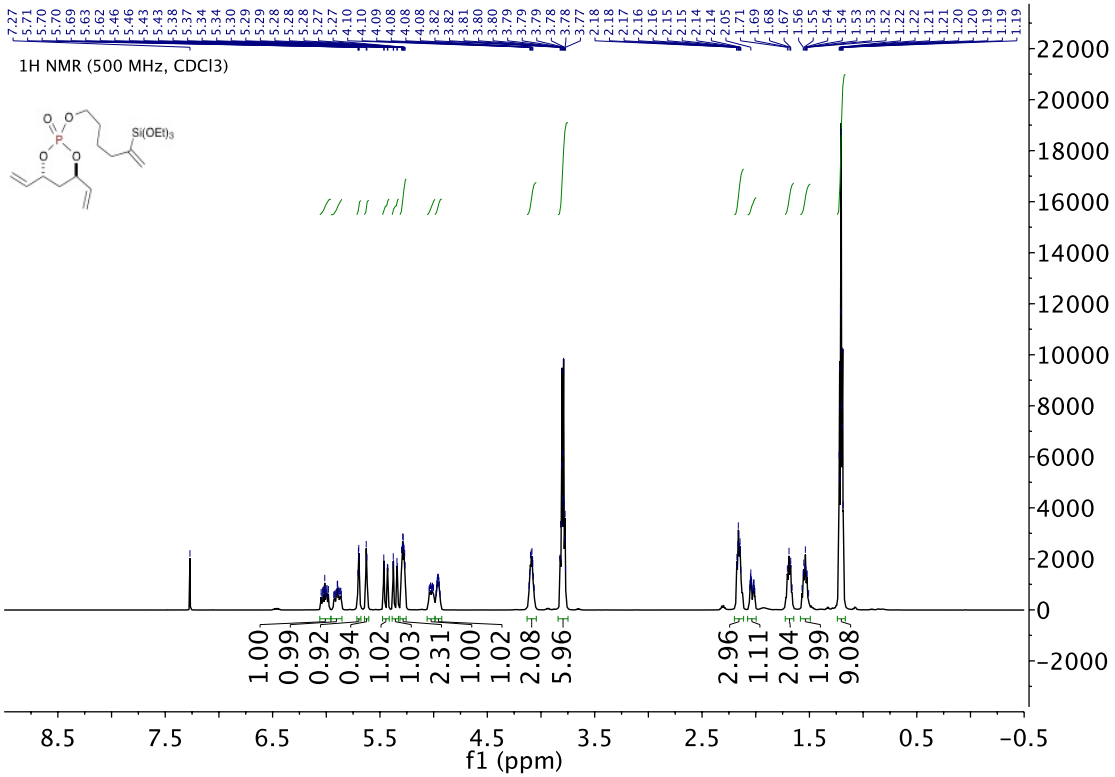

COSY (CDCl3)
1
2
3
4
5
6
7
8
f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)

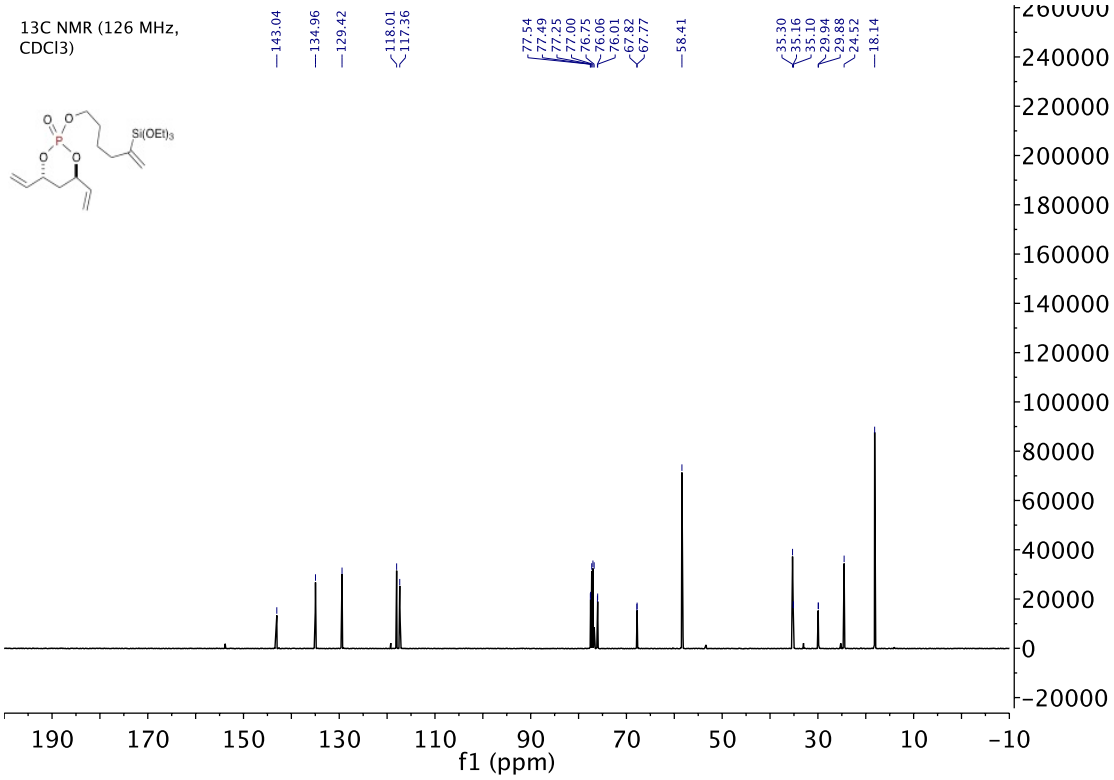

HSQC (CDCl3)
f2 (ppm)
f1 (ppm)
12
11
10
9
8
7
6
5
4
3
2
1
0
−1
−2
−3
−10
10
30
50
70
90
110
130
150

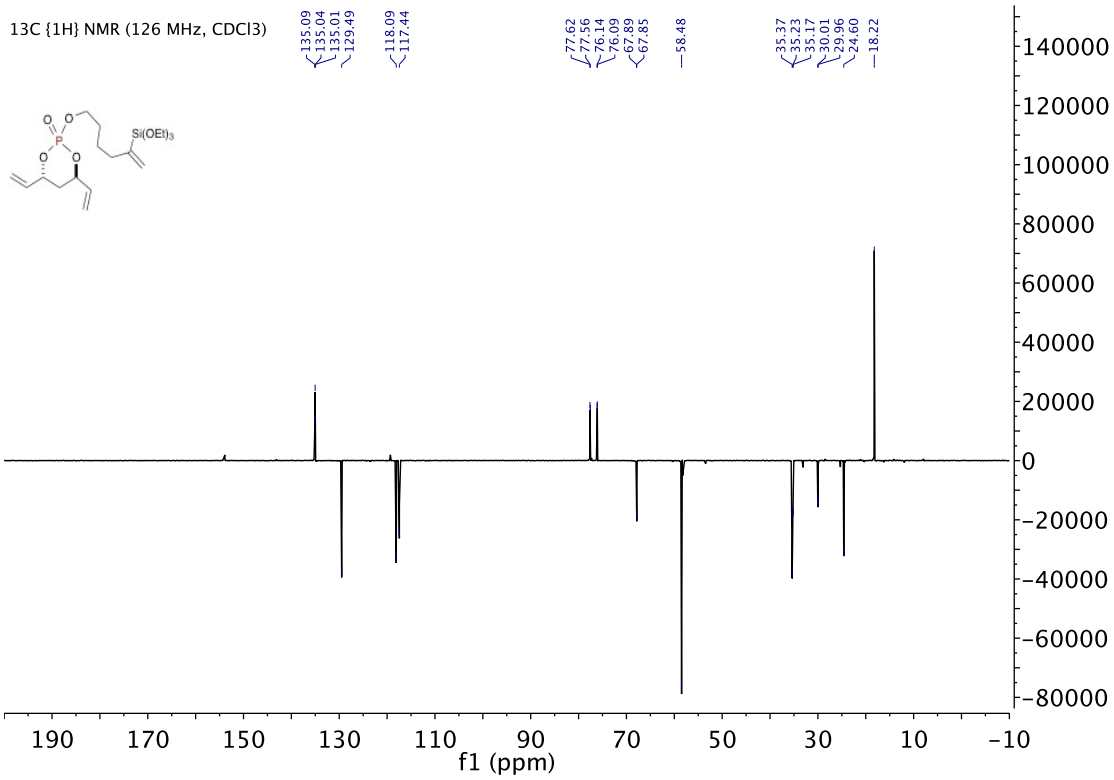
**(4*R*,6*R*)-2-((5-(triethoxysilyl)hex-5-en-1-yl)oxy)-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide (2.11.1)**

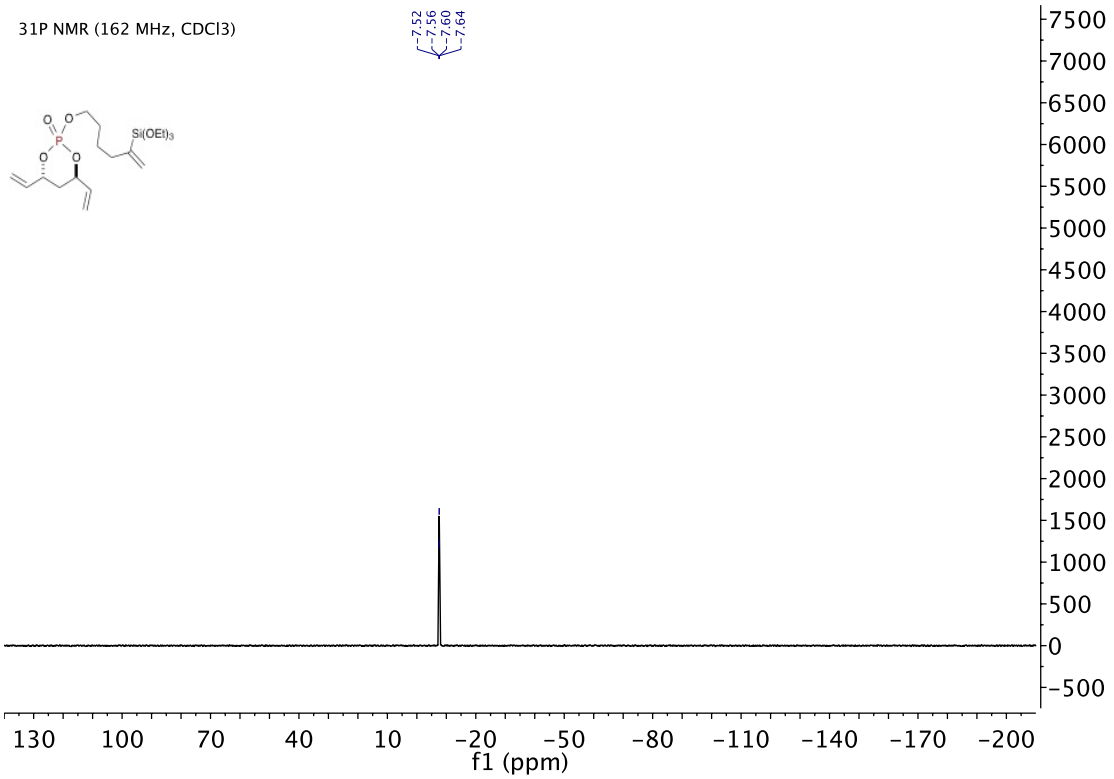


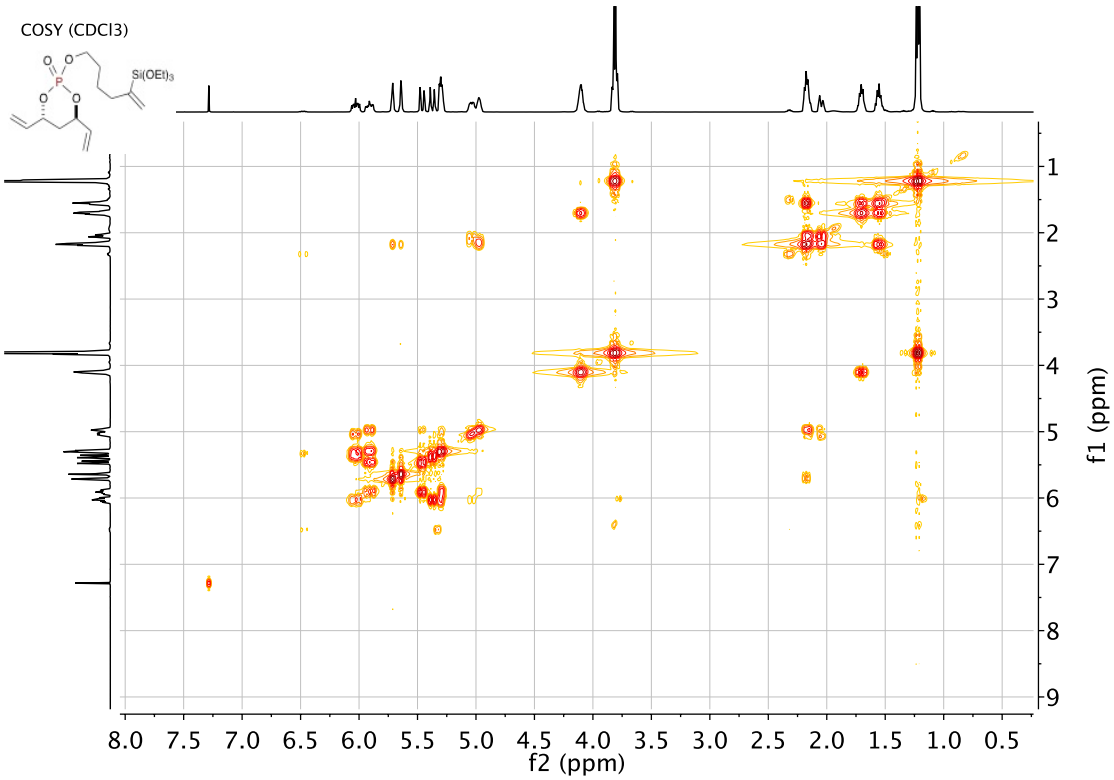

2.11.1

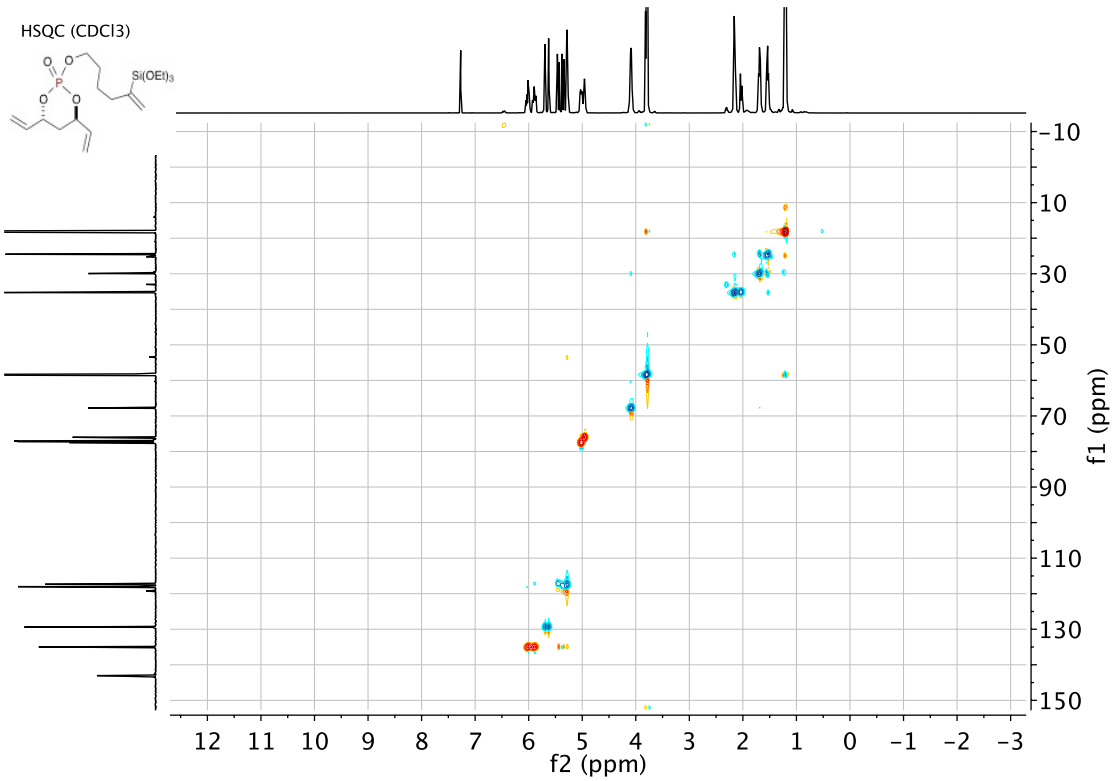



13C NMR (126 MHz, CDCl3)
143.04
134.96
129.42
118.01
117.36
77.54
77.49
77.25
77.00
76.75
76.06
76.01
67.82
67.77
58.41
35.30
35.16
35.10
29.94
29.88
24.52
18.14
Si(OEt)3
f1 (ppm)

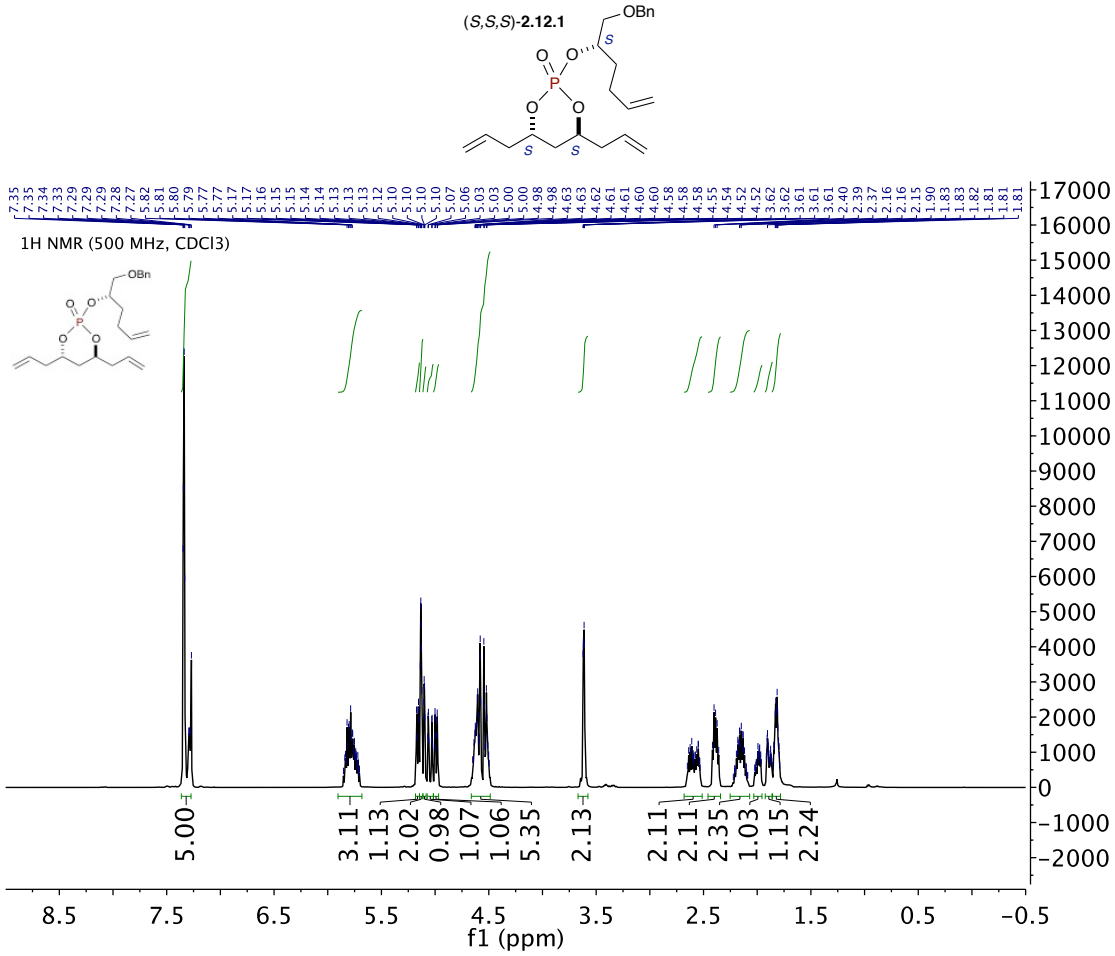

13C {1H} NMR (126 MHz, CDCl3)
135.09
135.04
135.01
129.49
118.09
117.44
77.62
77.56
76.14
76.09
67.89
67.85
58.48
35.37
35.23
35.17
30.01
29.96
24.60
18.22
Si(OEt)3
f1 (ppm)

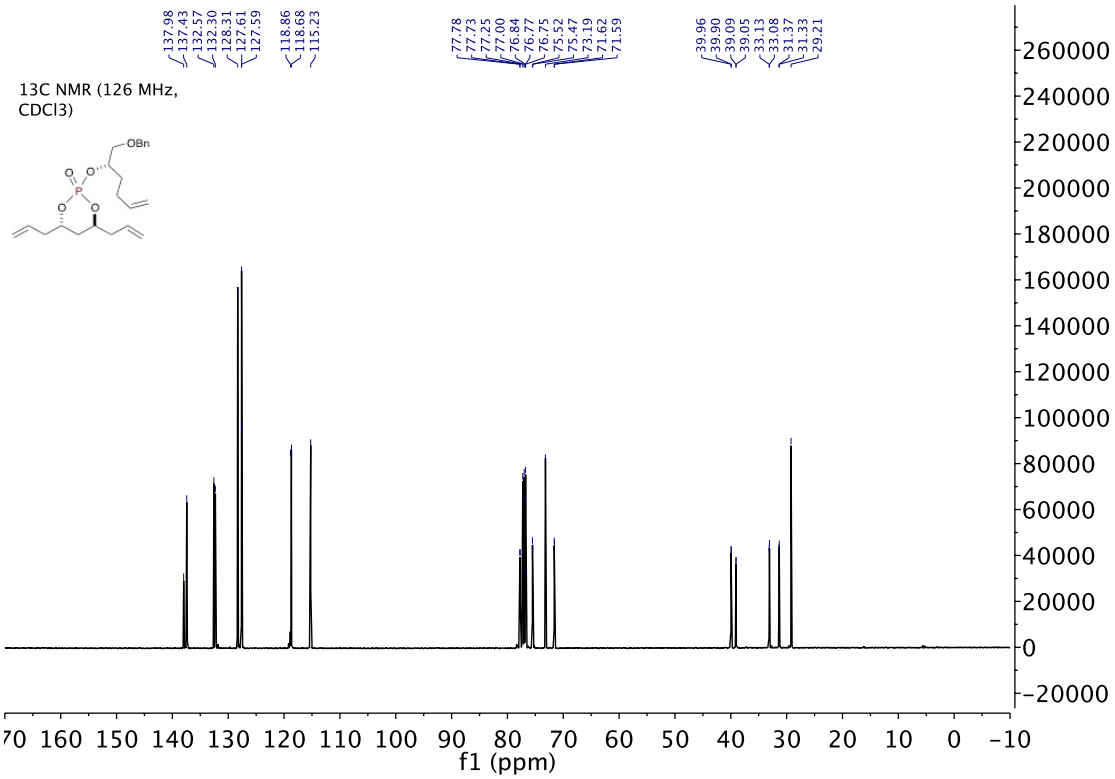

31P NMR (162 MHz, CDCl3)
7.52
7.56
7.60
7.64
Si(OEt)3
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
−500
130
100
70
40
10
−20
−50
−80
−110
−140
−170
−200
f1 (ppm)

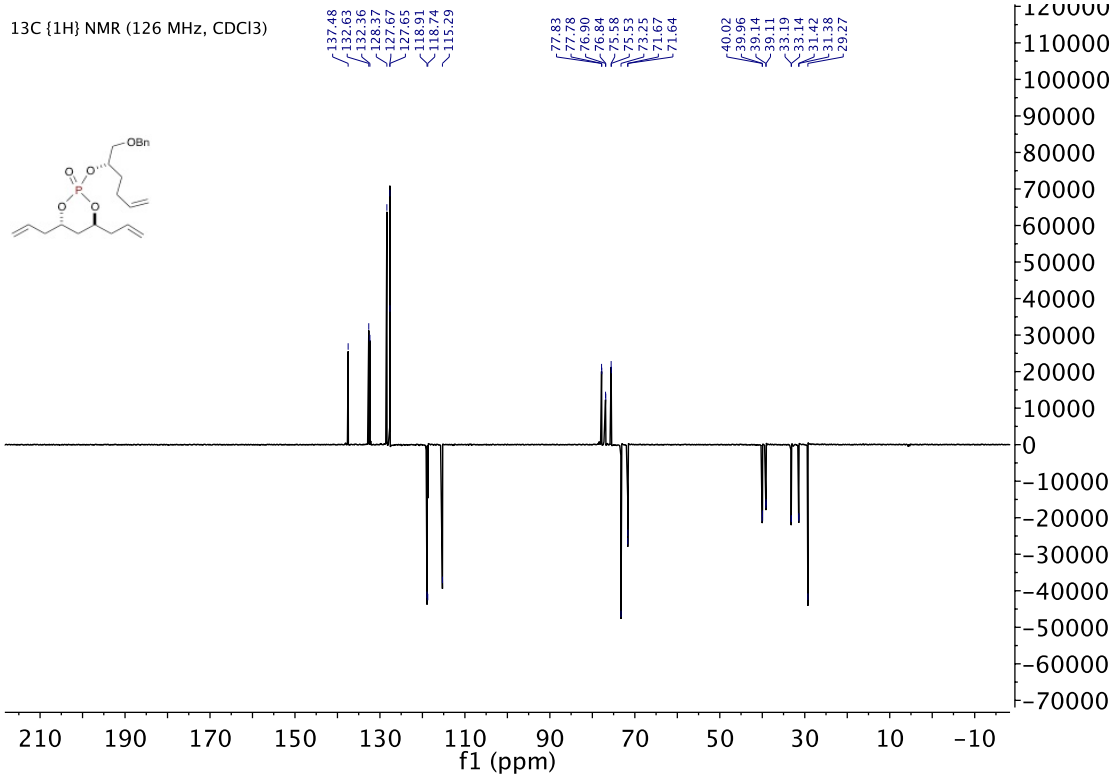

COSY (CDCl3)
Si(OEt)3
1
2
3
4
5
6
7
8
9
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)

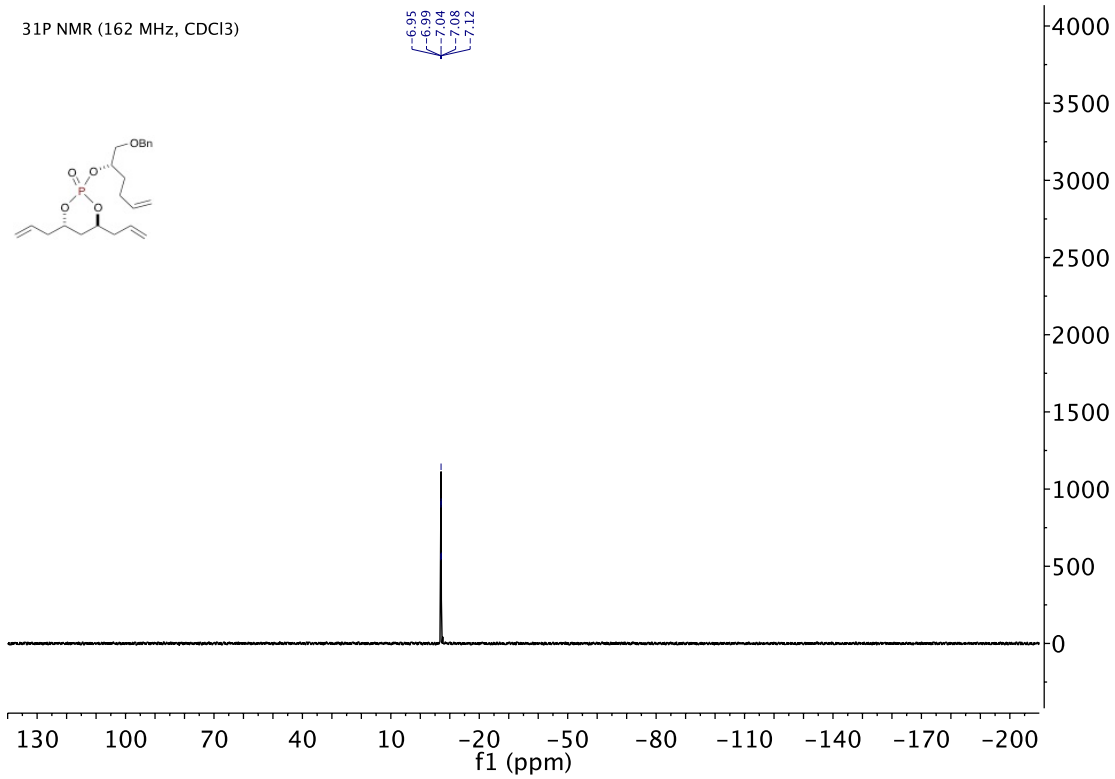

HSQC (CDCl3)
Si(OEt)3
f2 (ppm)
f1 (ppm)
12 11 10 9 8 7 6 5 4 3 2 1 0 −1 −2 −3
−10 10 30 50 70 90 110 130 150

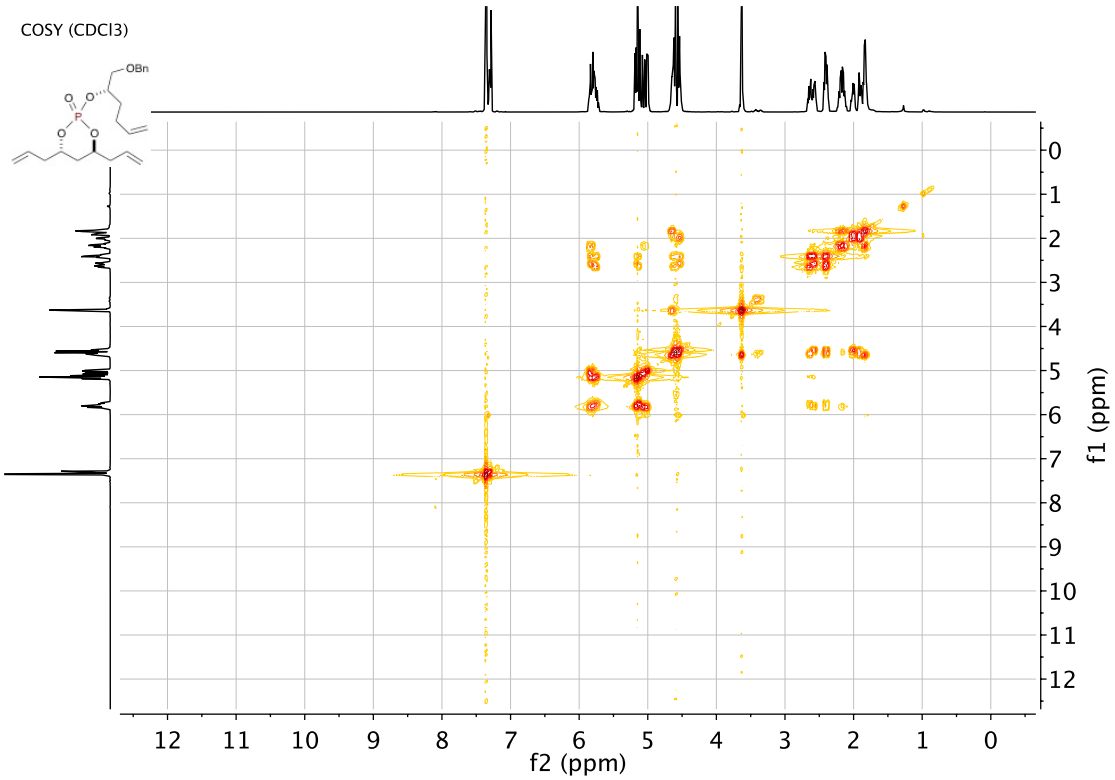
**(4*S*,6*S*)-4,6-diallyl-2-(((*S*)-1-(benzyloxy)hex-5-en-2-yl)oxy)-1,3,2-dioxaphosphinane 2-oxide (2.12.1)**

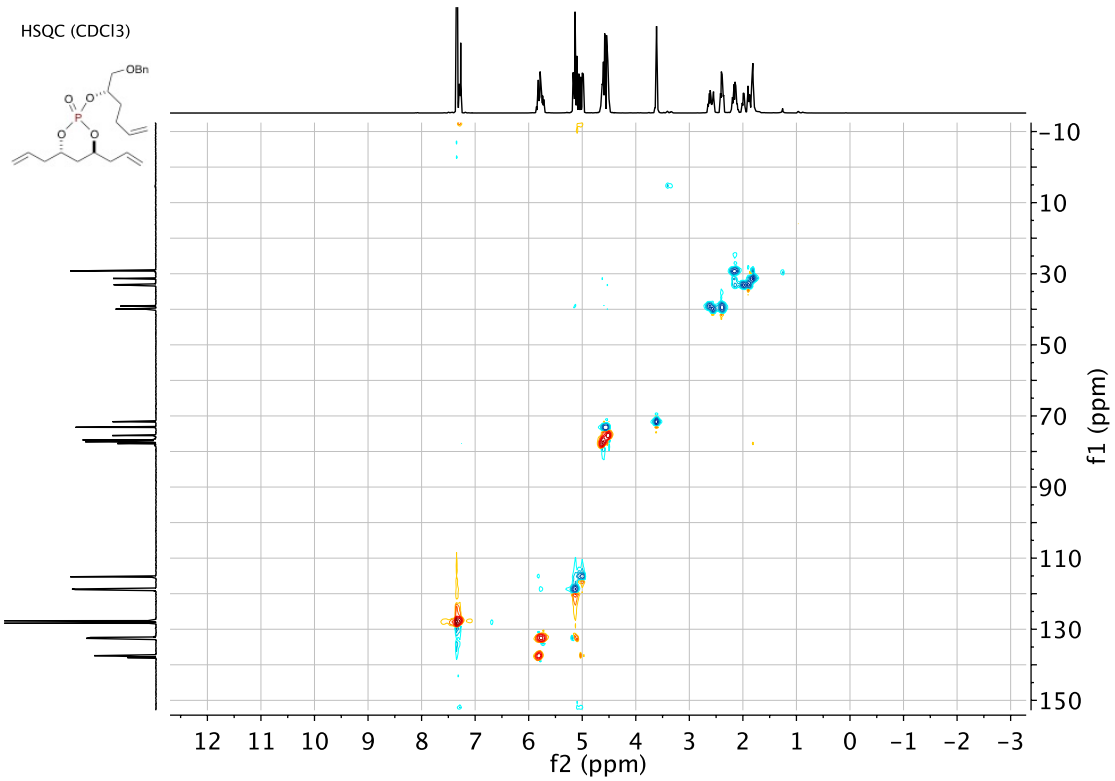



13C NMR (126 MHz, CDCl3)
137.98
137.43
132.57
132.30
128.31
127.61
127.59
118.86
118.68
115.23
77.78
77.73
77.25
77.00
76.84
76.77
76.75
75.52
75.47
73.19
71.62
71.59
39.96
39.90
39.09
39.05
33.13
33.08
31.37
31.33
29.21
OBn
f1 (ppm)

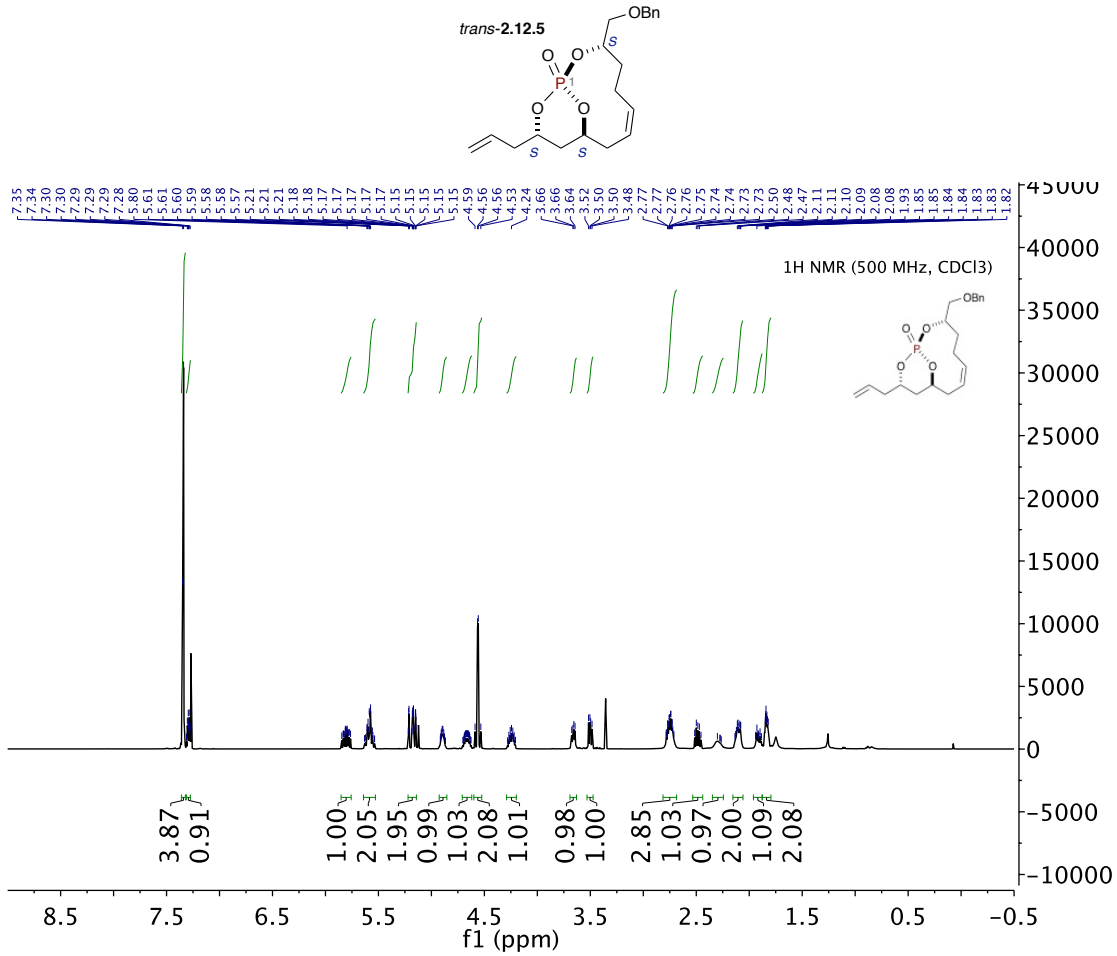

13C {1H} NMR (126 MHz, CDCl3)
137.48
132.63
132.36
128.37
127.67
127.65
118.91
118.74
115.29
77.83
77.78
76.90
76.84
75.58
75.53
73.25
71.67
71.64
40.02
39.96
39.14
39.11
33.19
33.14
31.42
31.38
29.27
OBn
f1 (ppm)

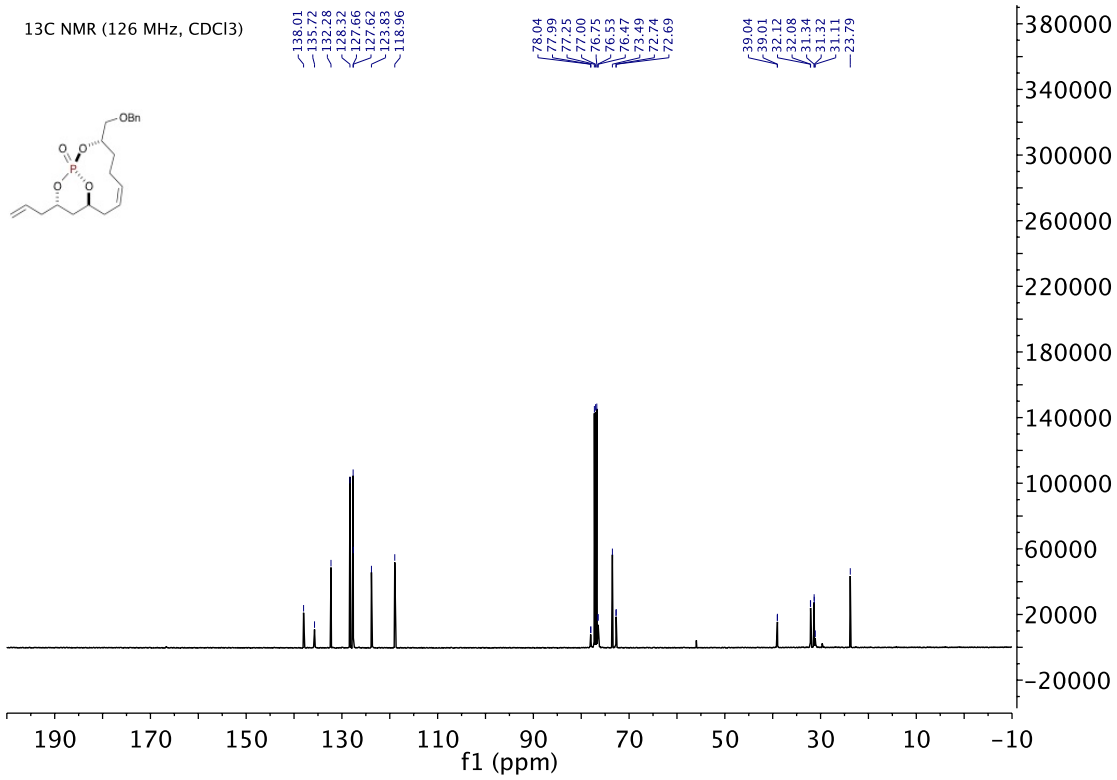

31P NMR (162 MHz, CDCl3)
6.95
6.99
7.04
7.08
7.12
OBn
4000
3500
3000
2500
2000
1500
1000
500
0
130
100
70
40
10
-20
-50
-80
-110
-140
-170
-200
f1 (ppm)

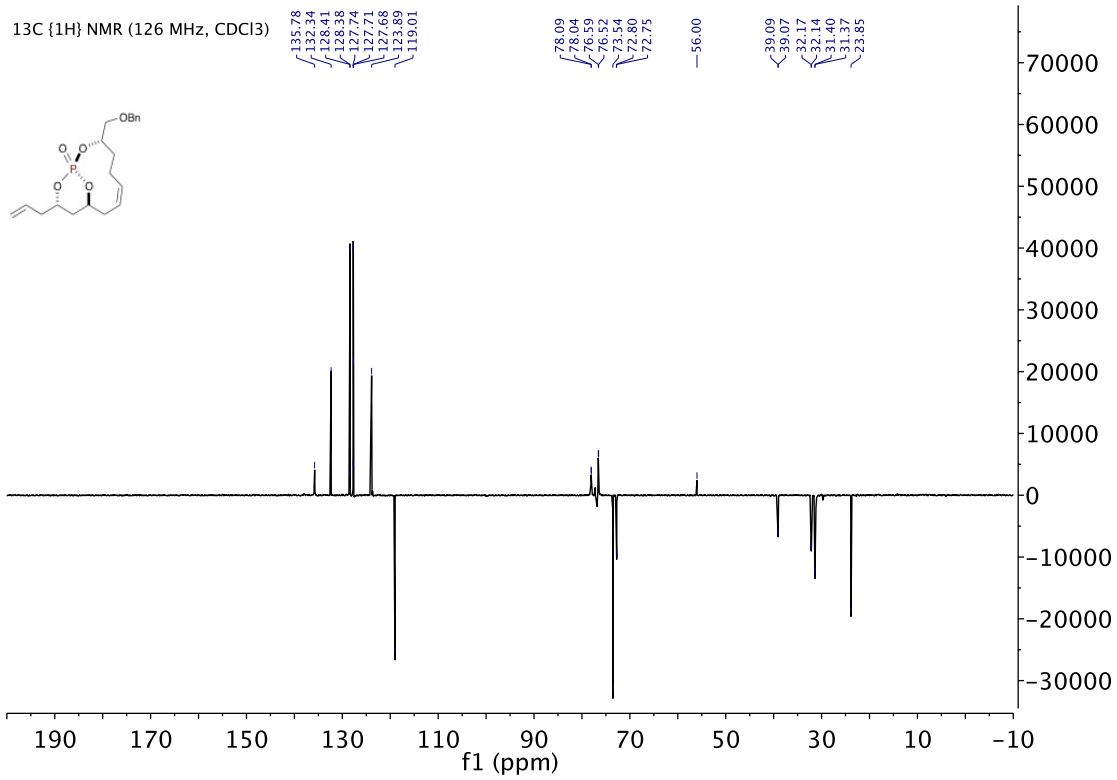

COSY (CDCl3)
OBn
0
1
2
3
4
5
6
7
8
9
10
11
12
f1 (ppm)
12
11
10
9
8
7
6
5
4
3
2
1
0
f2 (ppm)

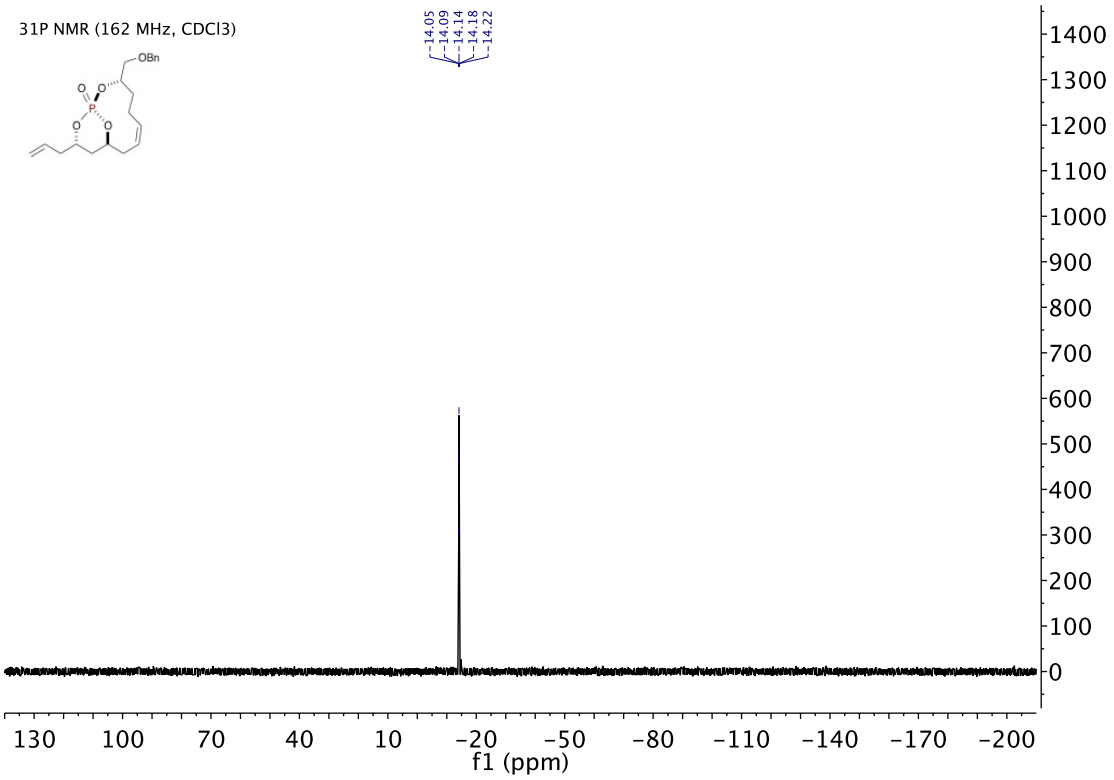

HSQC (CDCl3)
OBn
f2 (ppm)
f1 (ppm)
12
11
10
9
8
7
6
5
4
3
2
1
0
−1
−2
−3
−10
10
30
50
70
90
110
130
150

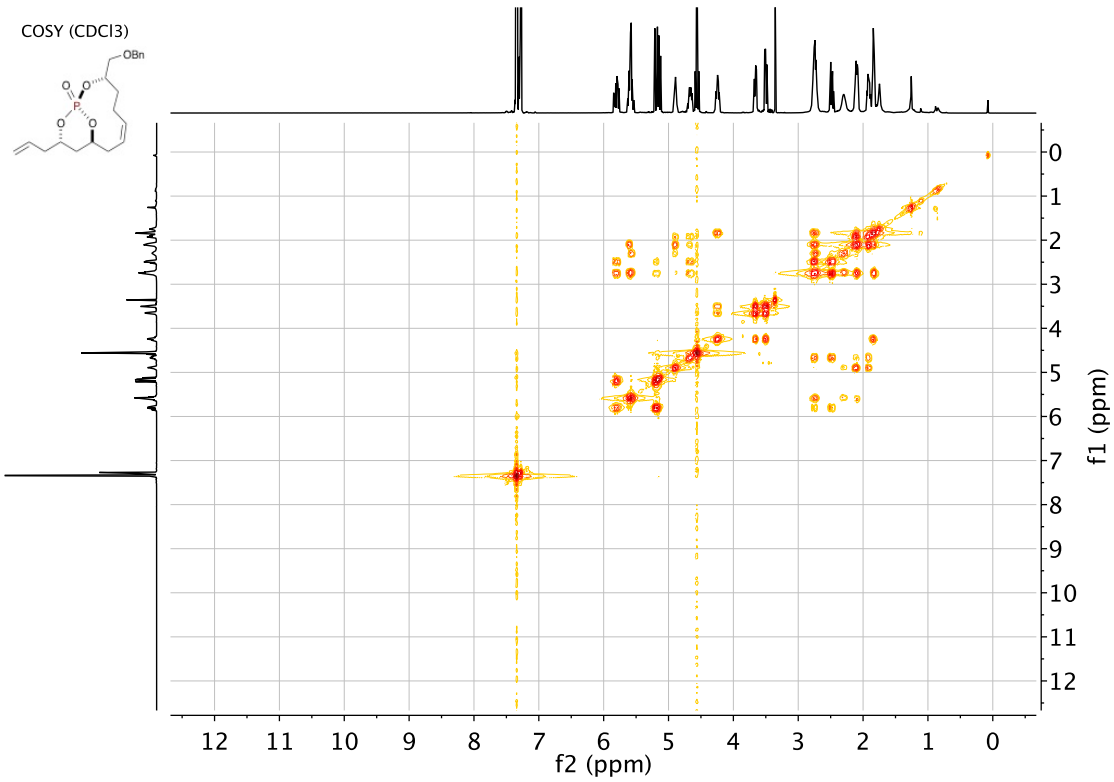
**(1*R*,3*S*,9*S*,11*S*,*Z*)-11-allyl-3-((benzyloxy)methyl)-2,12,13-trioxa-1-phosphabicyclo[7.3.1]tridec-6-ene 1-oxide (*trans*-2.12.5, *Z*-product)**

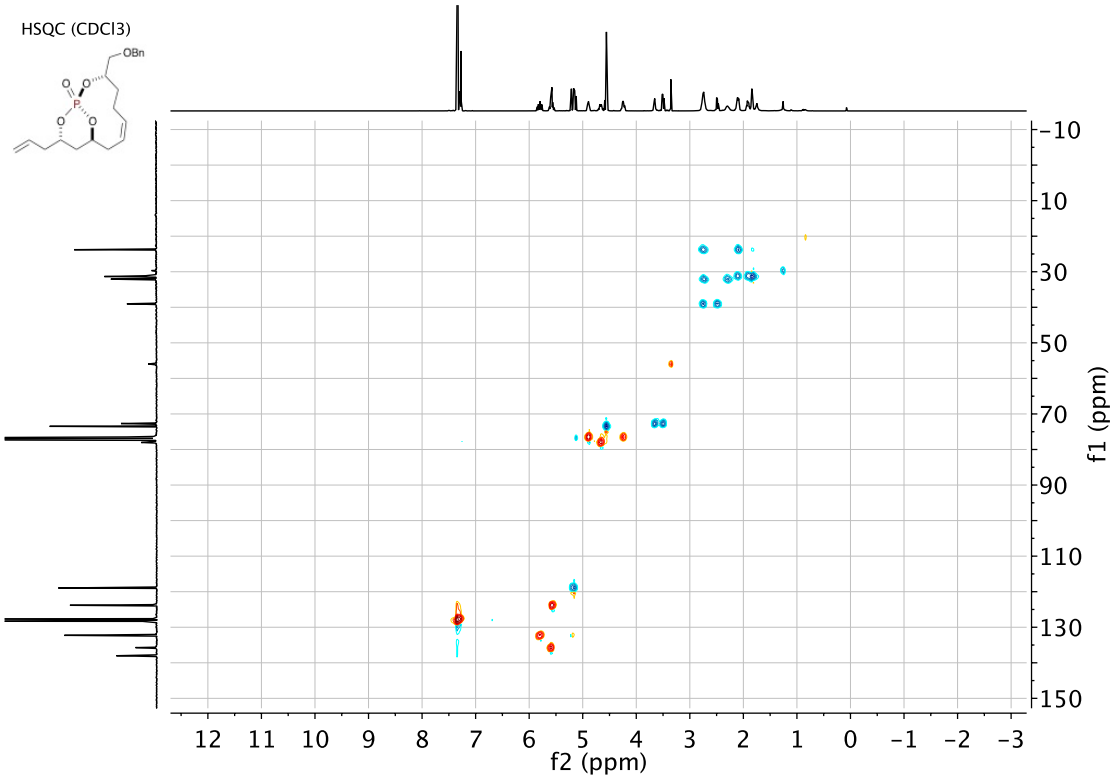


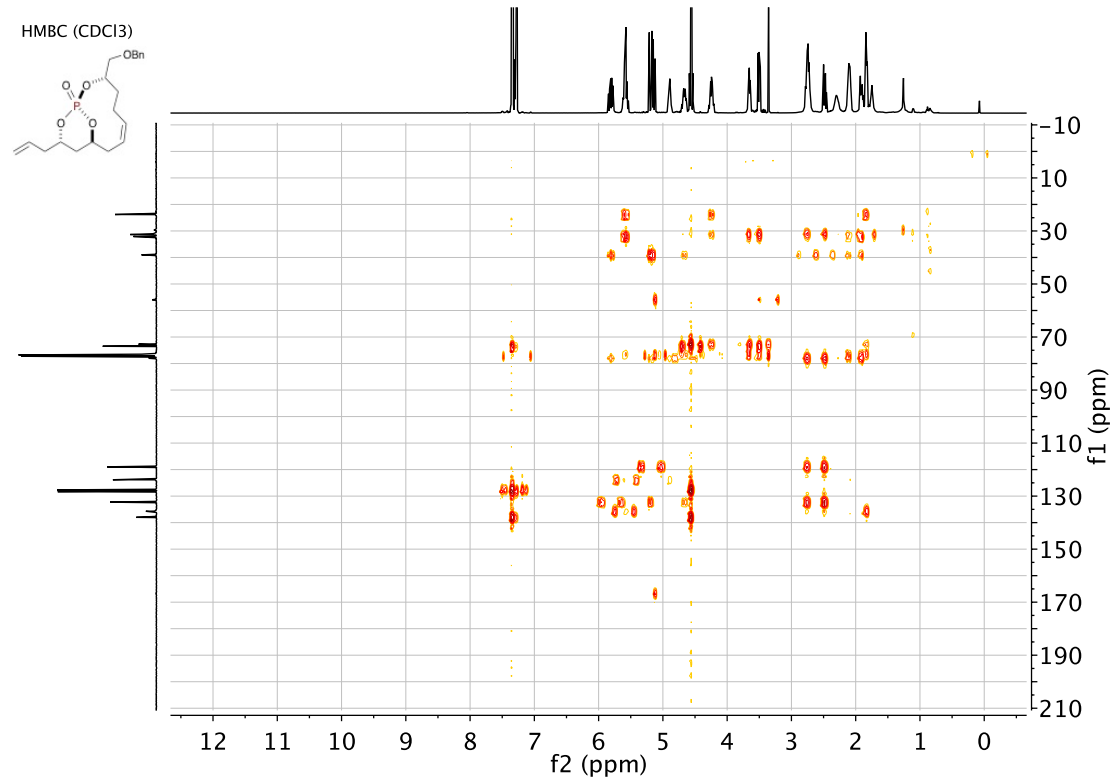

13C NMR (126 MHz, CDCl3)
138.01
135.72
132.28
128.32
127.66
127.62
123.83
118.96
78.04
77.99
77.25
77.00
76.75
76.53
76.47
73.49
72.74
72.69
39.04
39.01
32.12
32.08
31.34
31.32
31.11
23.79
OBn
380000
340000
300000
260000
220000
180000
140000
100000
60000
20000
-20000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

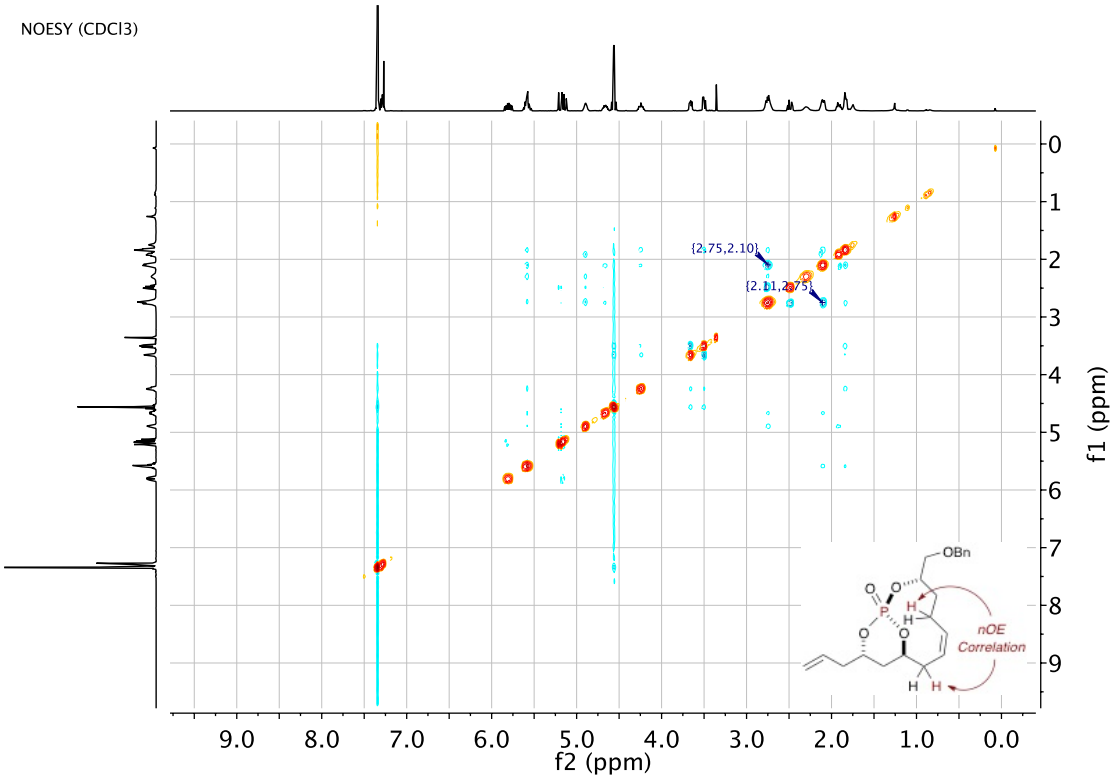

13C {1H} NMR (126 MHz, CDCl3)
135.78
132.34
128.41
128.38
127.74
127.71
127.68
123.89
119.01
78.09
78.04
76.59
76.52
73.54
72.80
72.75
56.00
39.09
39.07
32.17
32.14
31.40
31.37
23.85
OBn
70000
60000
50000
40000
30000
20000
10000
0
-10000
-20000
-30000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)


31P NMR (162 MHz, CDCl3)
OBn
14.05
14.09
14.14
14.18
14.22
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
130
100
70
40
10
-20
-50
-80
-110
-140
-170
-200
f1 (ppm)

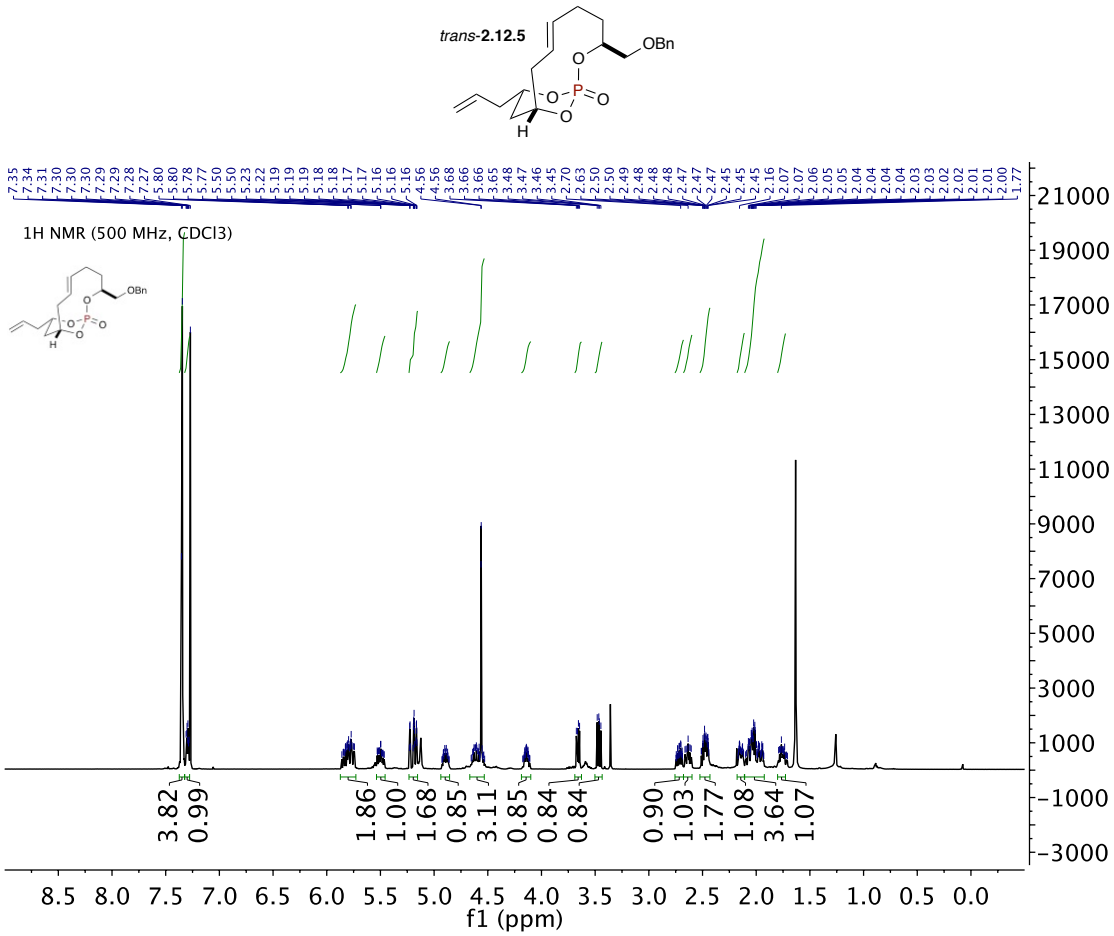

COSY (CDCl3)
OBn
0
1
2
3
4
5
6
7
8
9
10
11
12
f1 (ppm)
12
11
10
9
8
7
6
5
4
3
2
1
0
f2 (ppm)

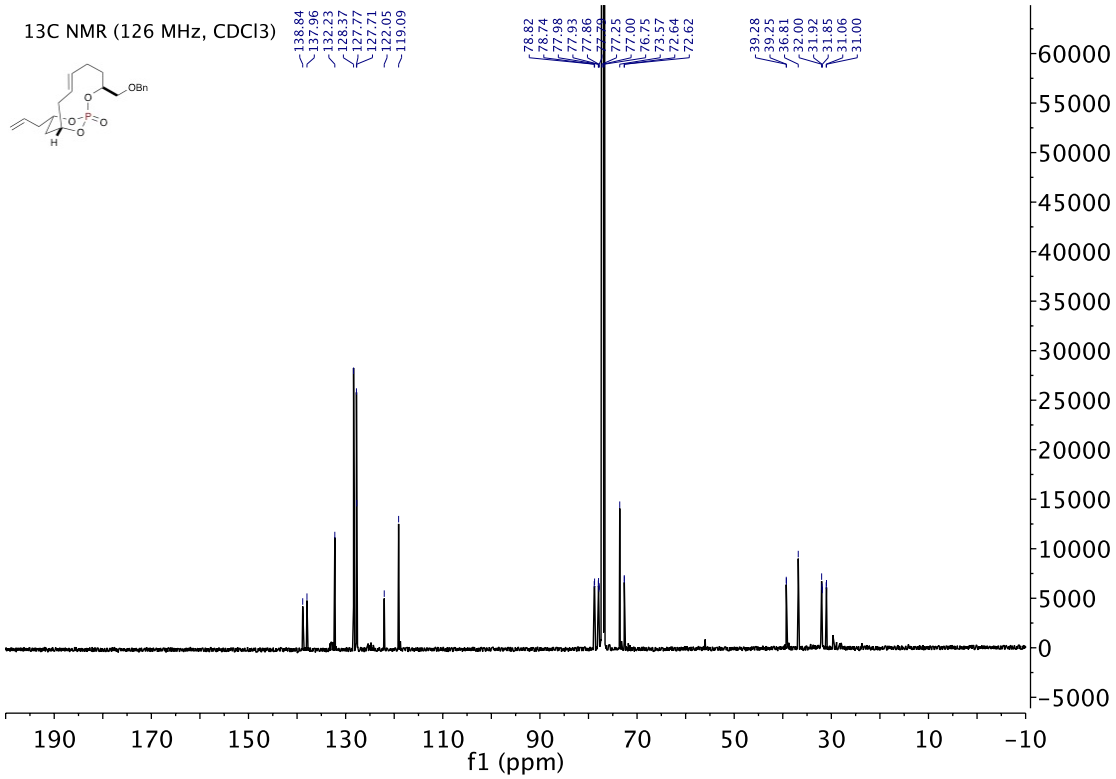

HSQC (CDCl3)
OBn
f2 (ppm)
f1 (ppm)

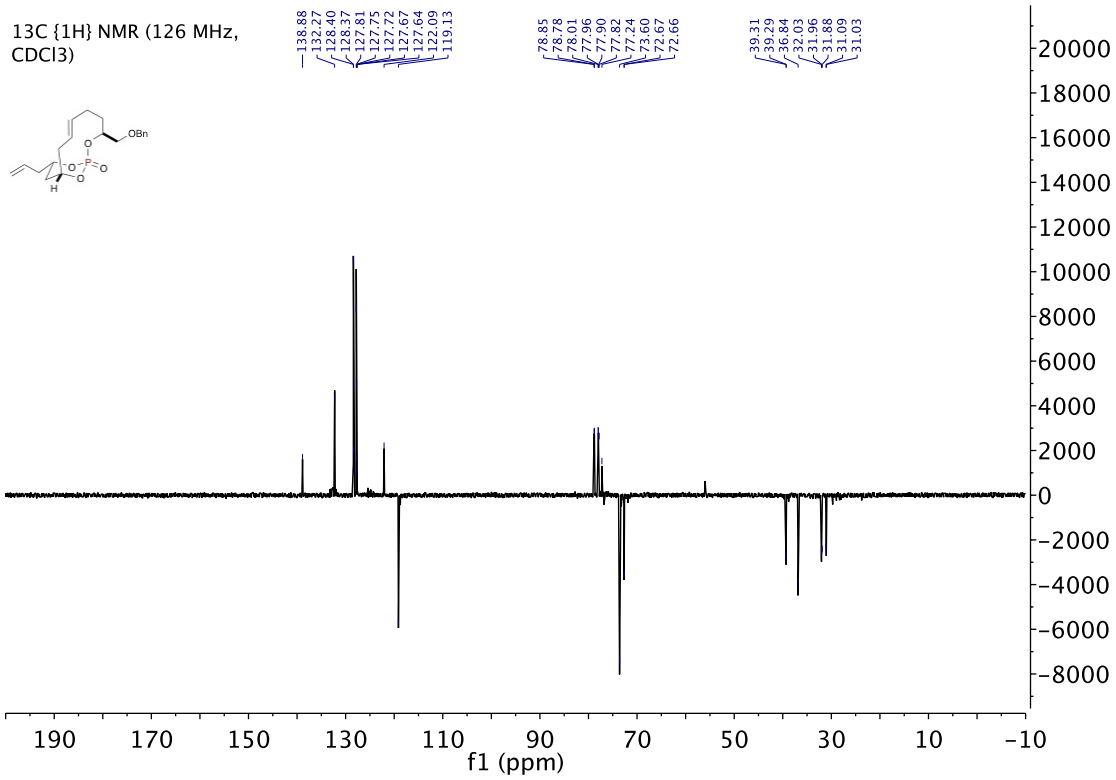

HMBC (CDCl3)
OBn
f2 (ppm)
f1 (ppm)

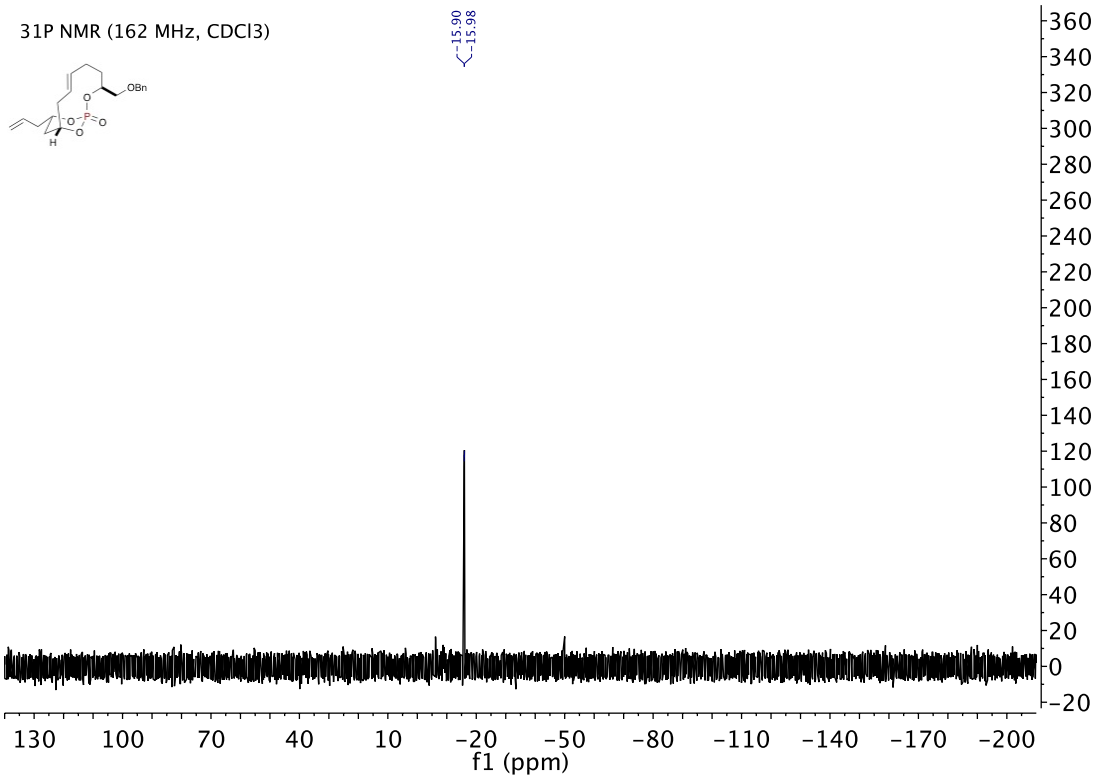

NOESY (CDCl3)
{2.75,2.10}
{2.11,2.75}
OBn
nOE
Correlation
f2 (ppm)
f1 (ppm)
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0
1
2
3
4
5
6
7
8
9

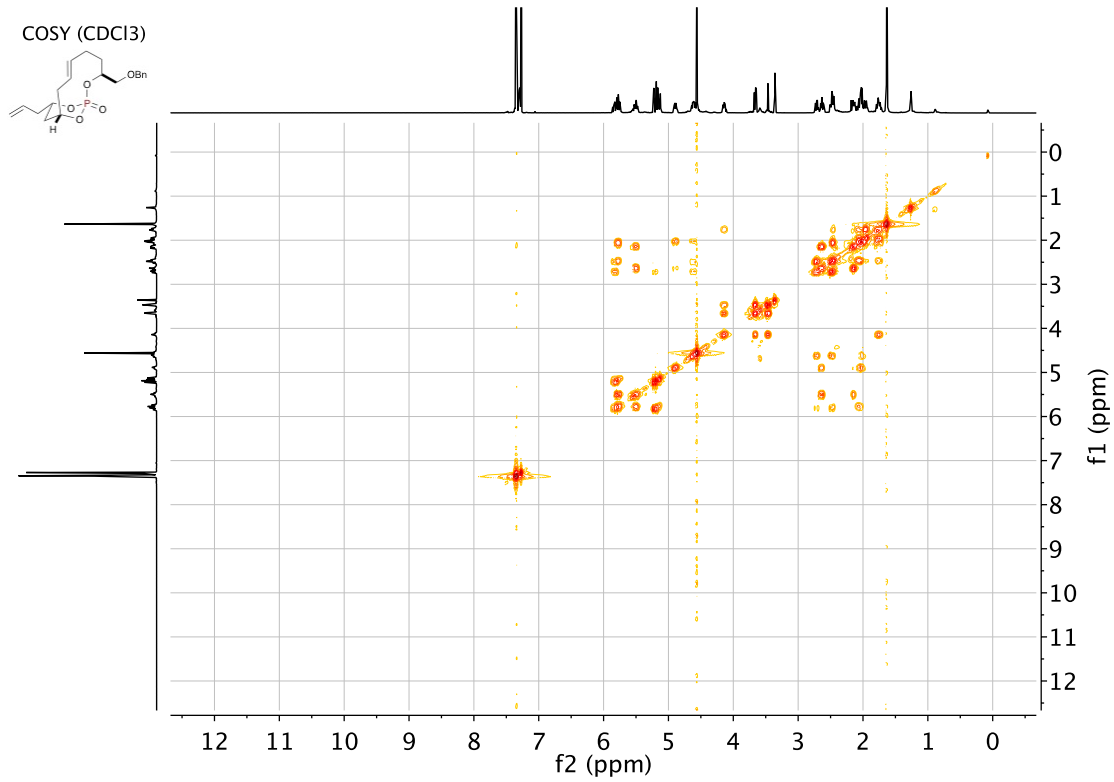
**(1*R*,3*S*,9*S*,11*S*,*E*)-11-allyl-3-((benzyloxy)methyl)-2,12,13-trioxa-1-phosphabicyclo[7.3.1]tridec-6-ene 1-oxide (*trans*-2.12.5, *E*-product)**

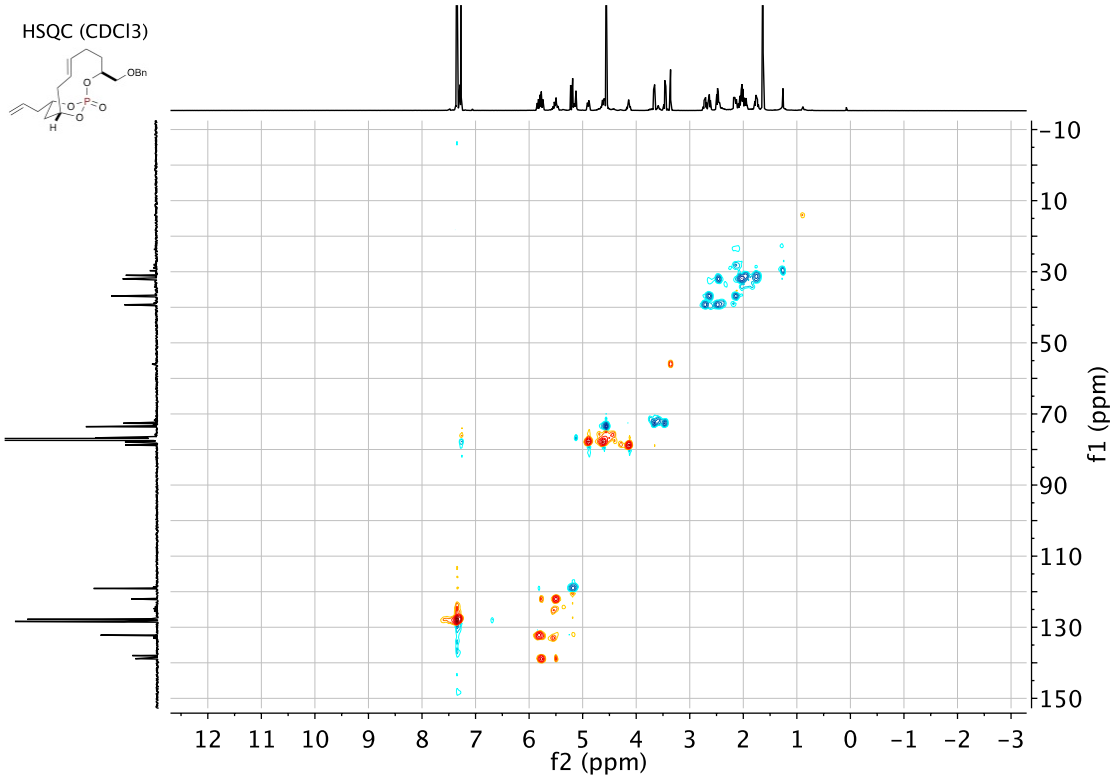


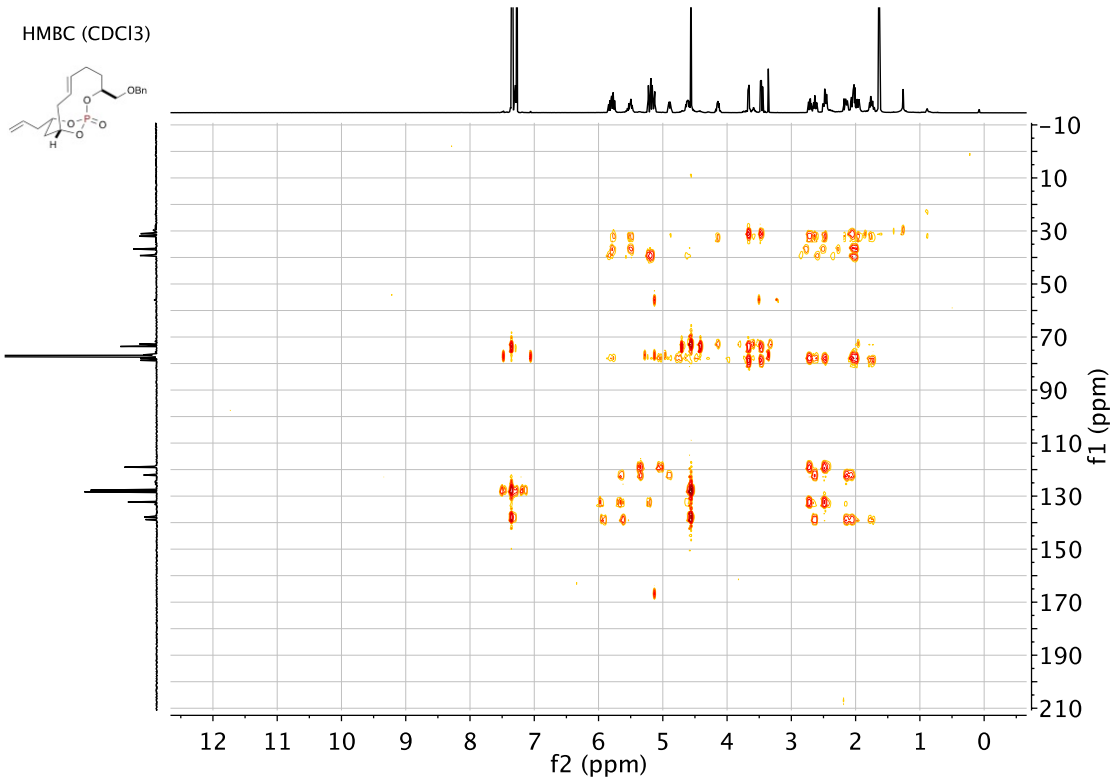

13C NMR (126 MHz, CDCl3)
138.84
137.96
132.23
128.37
127.77
127.71
122.05
119.09
78.82
78.74
77.98
77.93
77.86
77.25
77.00
76.75
73.57
72.64
72.62
39.28
39.25
36.81
32.00
31.92
31.85
31.06
31.00
OBn
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

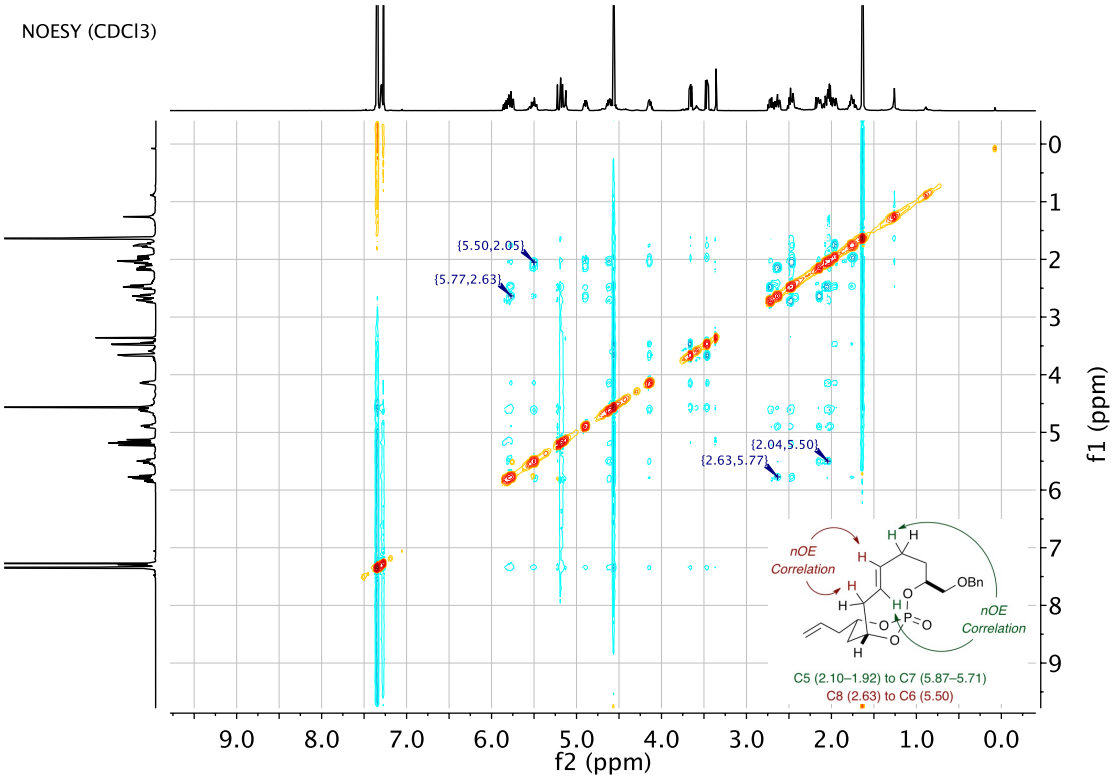

13C {1H} NMR (126 MHz, CDCl3)
138.88
132.27
128.40
128.37
127.81
127.75
127.72
127.67
127.64
122.09
119.13
78.85
78.78
78.01
77.96
77.90
77.82
77.24
73.60
72.67
72.66
39.31
39.29
36.84
32.03
31.96
31.88
31.09
31.03
OBn
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
-4000
-6000
-8000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)


31P NMR (162 MHz, CDCl3)
OBn
-15.90
-15.98
360
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
130
100
70
40
10
-20
-50
-80
-110
-140
-170
-200
f1 (ppm)

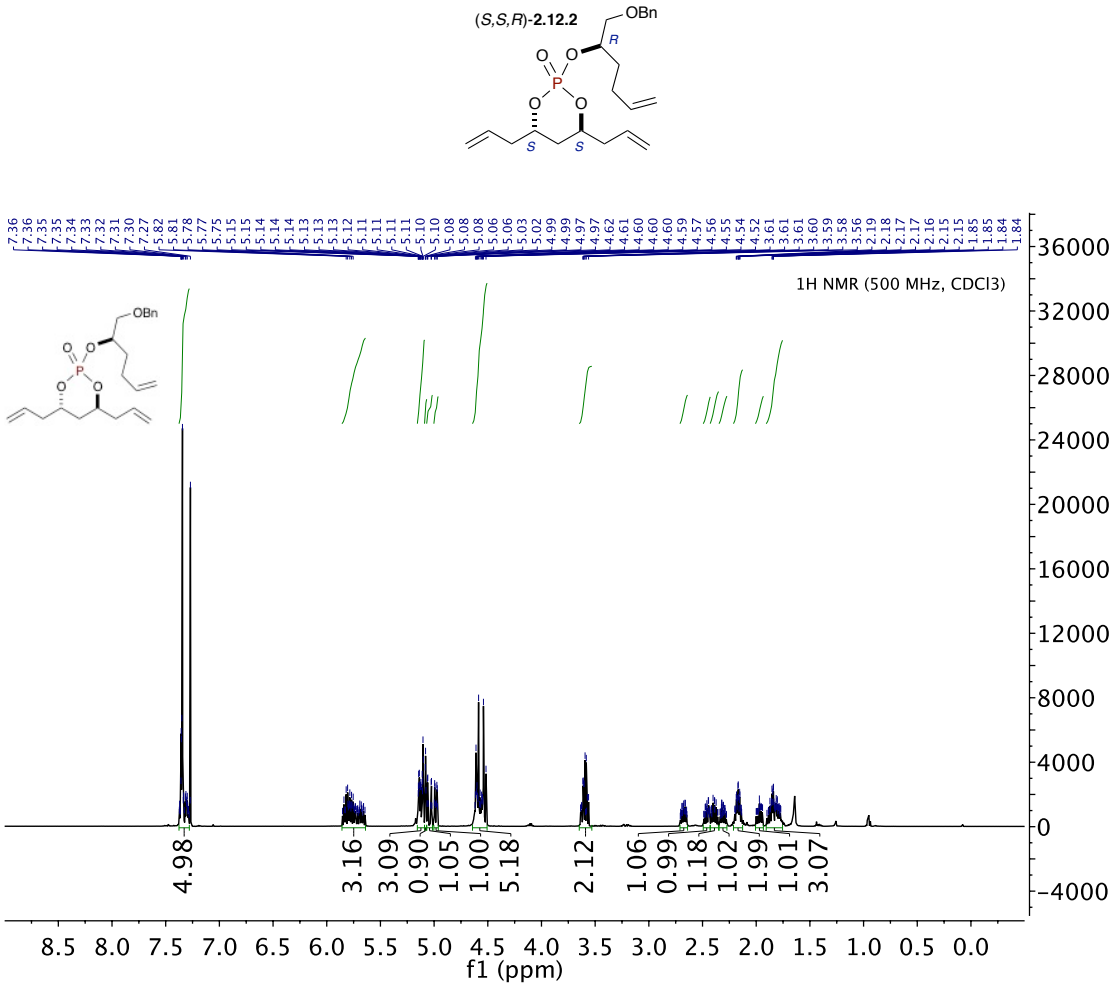

COSY (CDCl3)
OBn
0
1
2
3
4
5
6
7
8
9
10
11
12
f1 (ppm)
12
11
10
9
8
7
6
5
4
3
2
1
0
f2 (ppm)

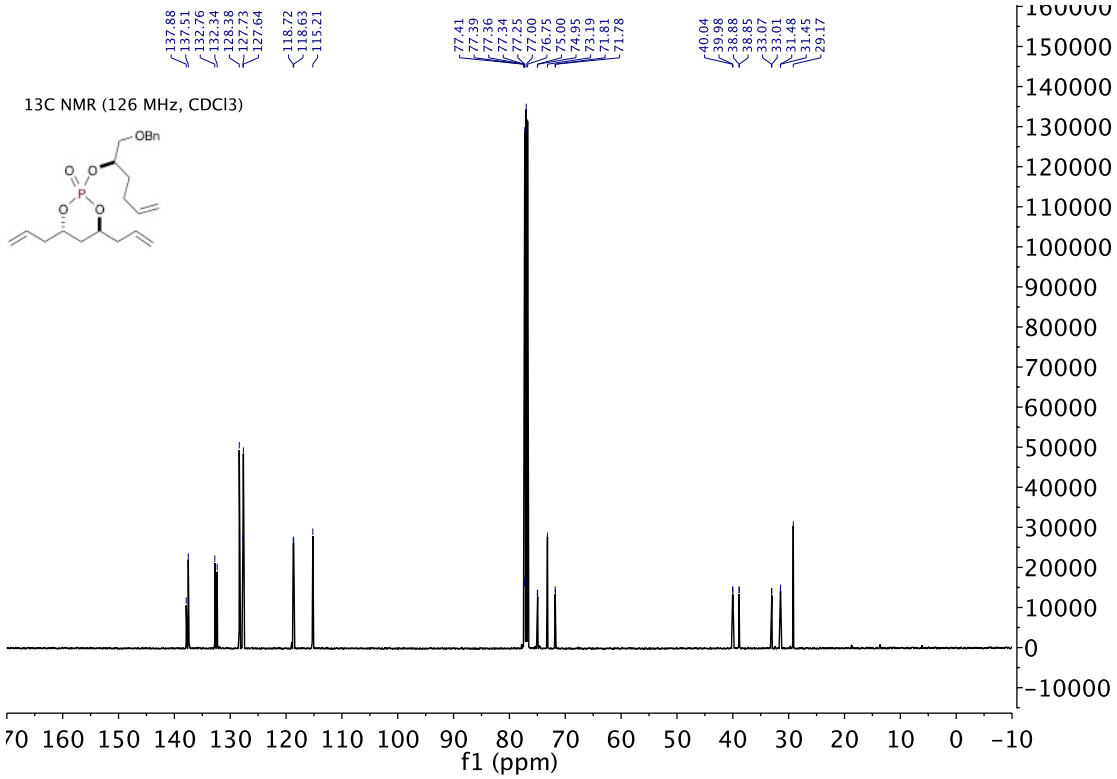

HSQC (CDCl3)
OBn
12 11 10 9 8 7 6 5 4 3 2 1 0 −1 −2 −3
f2 (ppm)
−10 10 30 50 70 90 110 130 150
f1 (ppm)

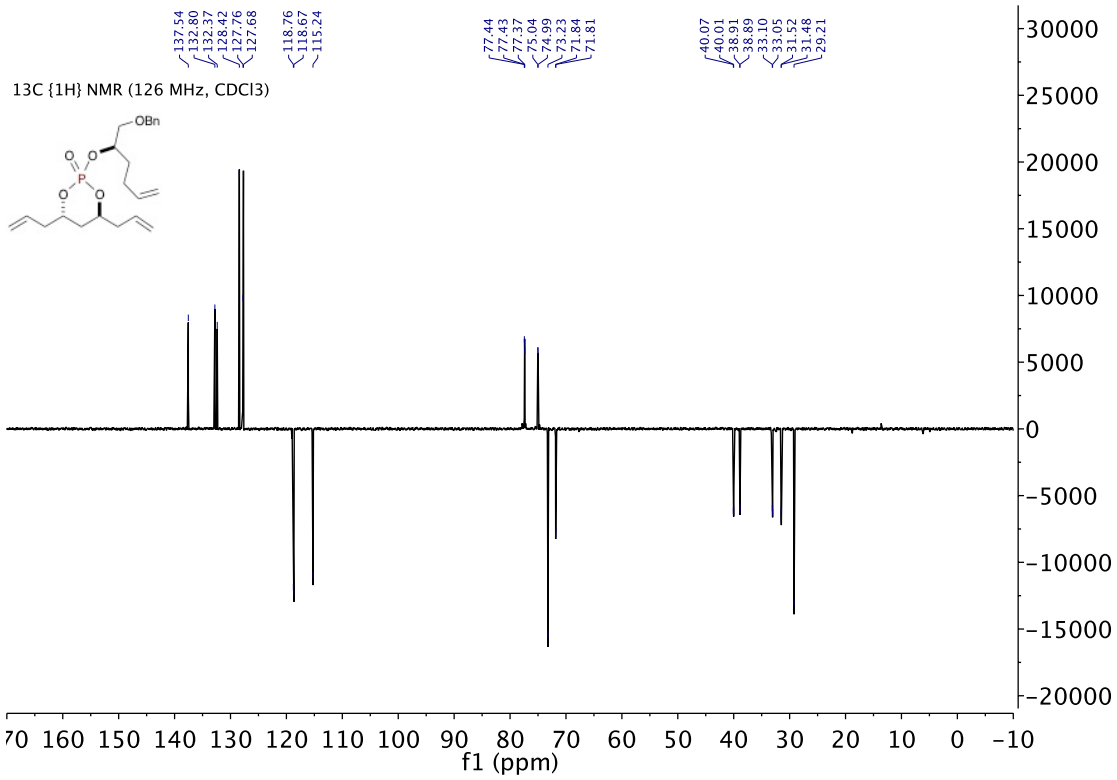

HMBC (CDCl3)
OBn
12 11 10 9 8 7 6 5 4 3 2 1 0
f2 (ppm)
−10 10 30 50 70 90 110 130 150 170 190 210
f1 (ppm)

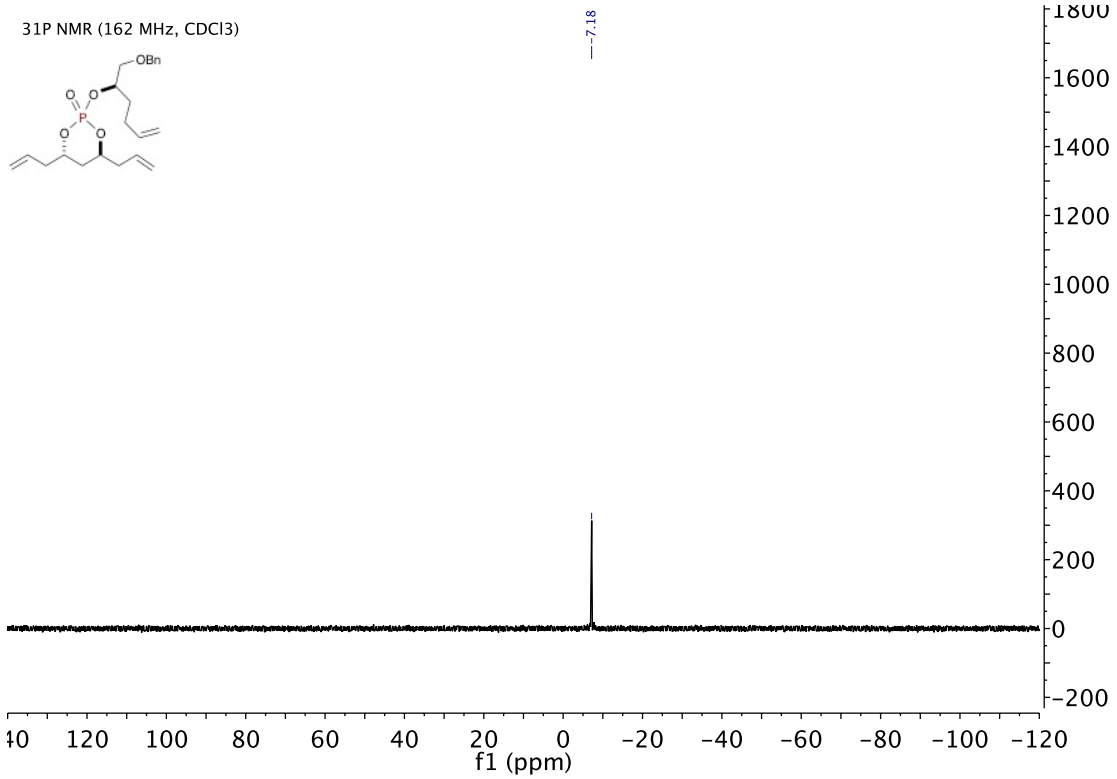

NOESY (CDCl3)
{5.50,2.05}
{5.77,2.63}
{2.04,5.50}
{2.63,5.77}
nOE
Correlation
nOE
Correlation
OBn
C5 (2.10–1.92) to C7 (5.87–5.71)
C8 (2.63) to C6 (5.50)
f2 (ppm)
f1 (ppm)

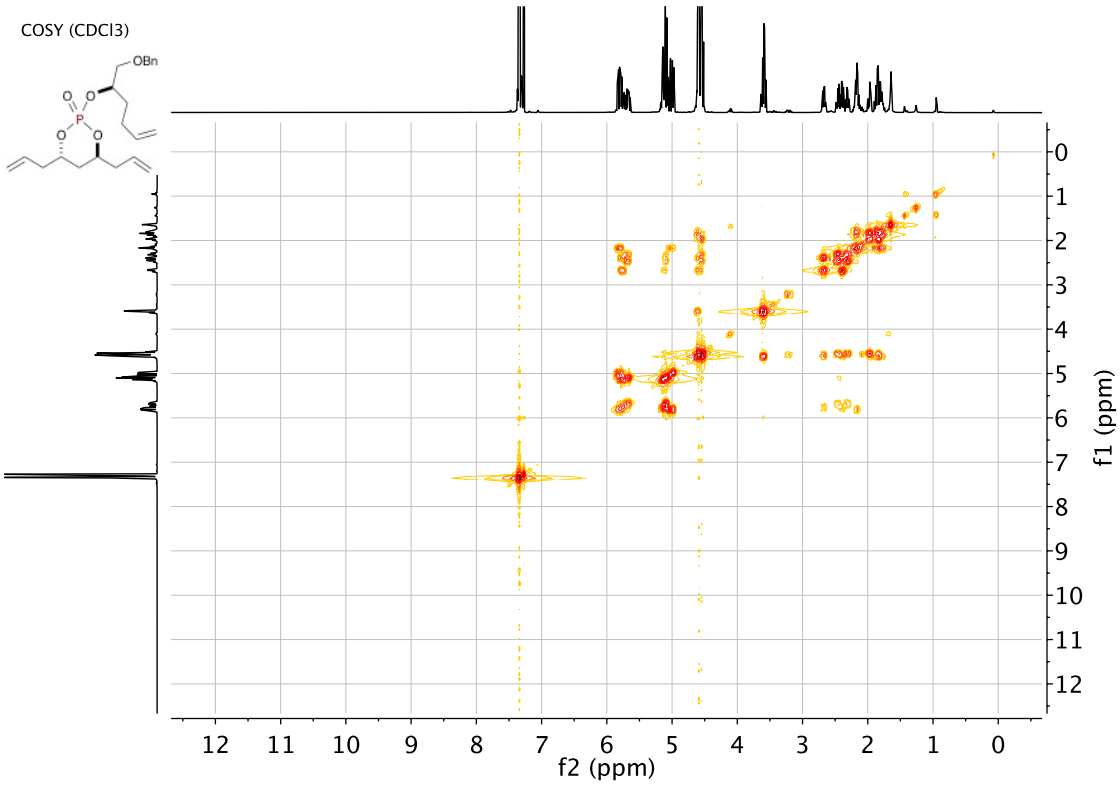
**(4*S*,6*S*)-4,6-diallyl-2-(((*R*)-1-(benzyloxy)hex-5-en-2-yl)oxy)-1,3,2-dioxaphosphinane 2-oxide (2.12.2)**

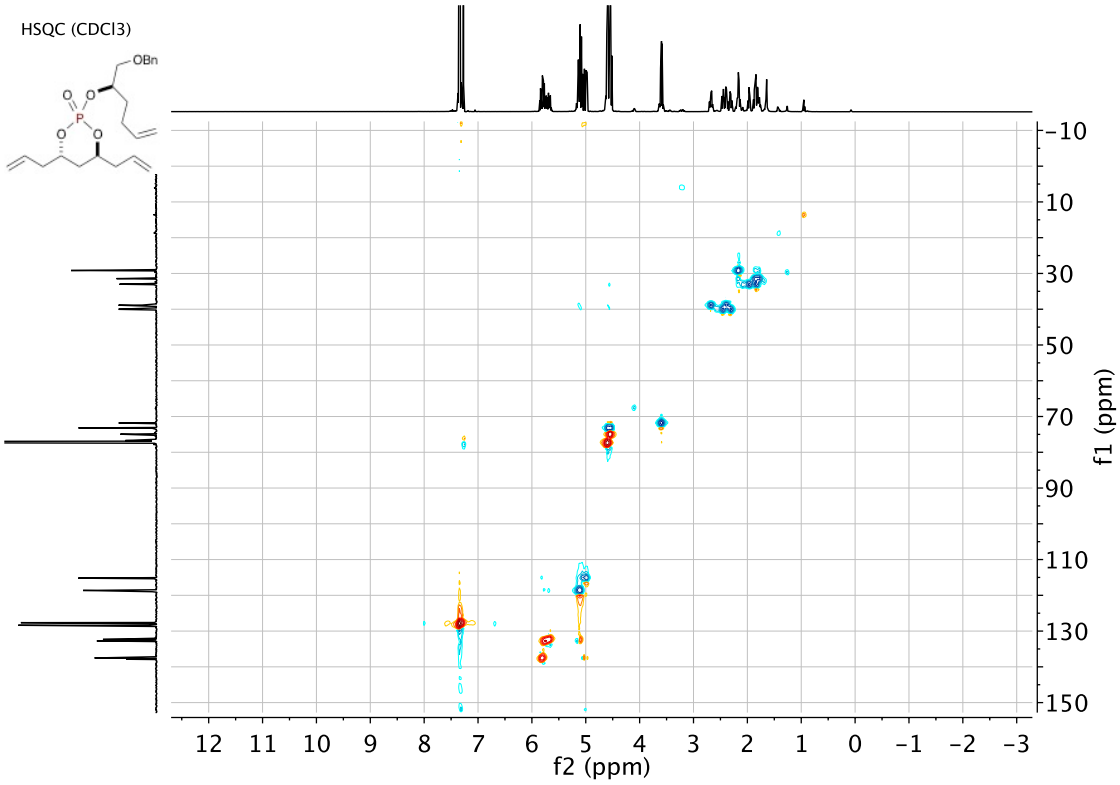



137.88
137.51
132.76
132.34
128.38
127.73
127.64
118.72
118.63
115.21
77.41
77.39
77.36
77.34
77.25
77.00
76.75
75.00
74.95
73.19
71.81
71.78
40.04
39.98
38.88
38.65
33.07
33.01
31.48
31.45
29.17
13C NMR (126 MHz, CDCl3)
OBn
f1 (ppm)

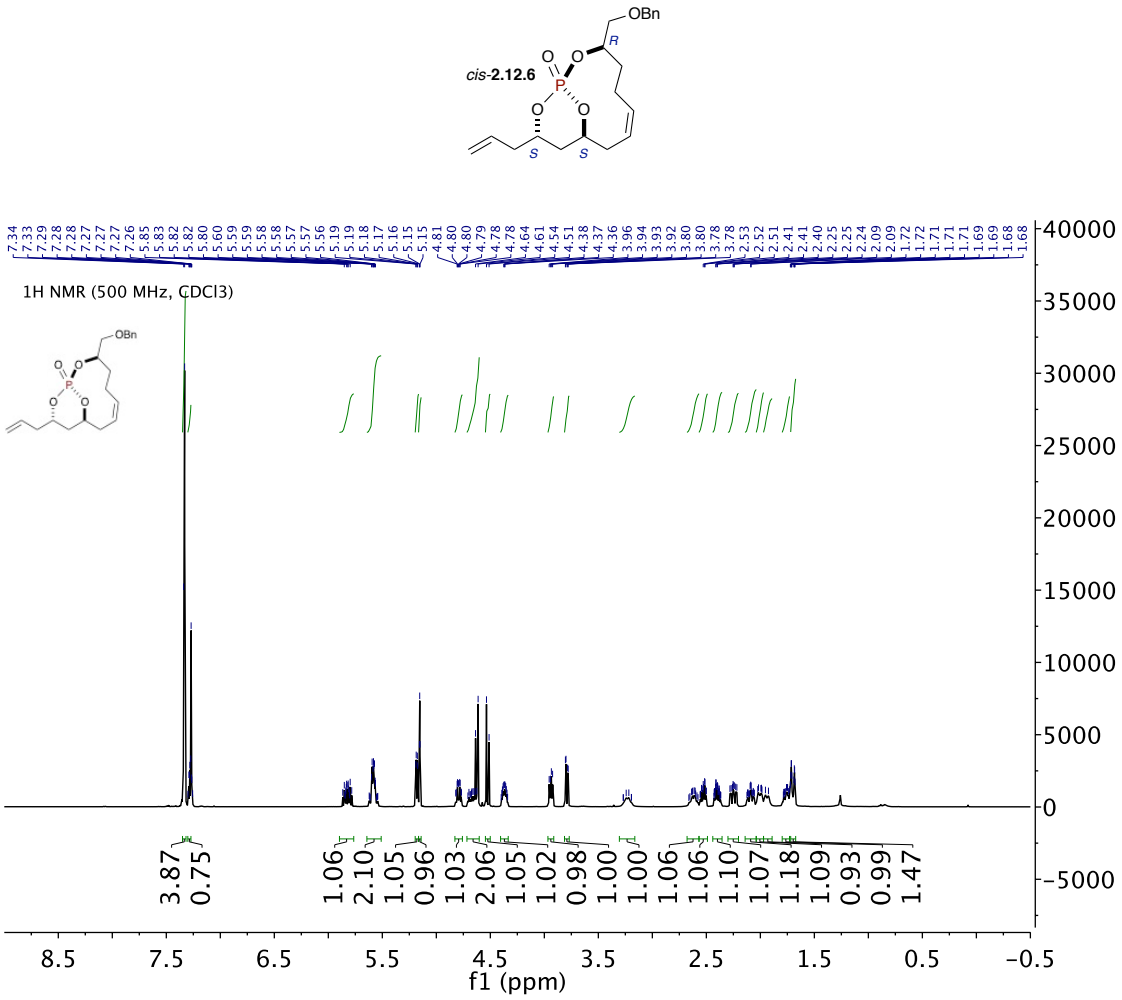

137.54
132.80
132.37
128.42
127.76
127.68
118.76
118.67
115.24
77.44
77.43
77.37
75.04
74.99
73.23
71.84
71.81
40.07
40.01
38.91
38.89
33.10
33.05
31.52
31.48
29.21
13C {1H} NMR (126 MHz, CDCl3)
OBn
f1 (ppm)

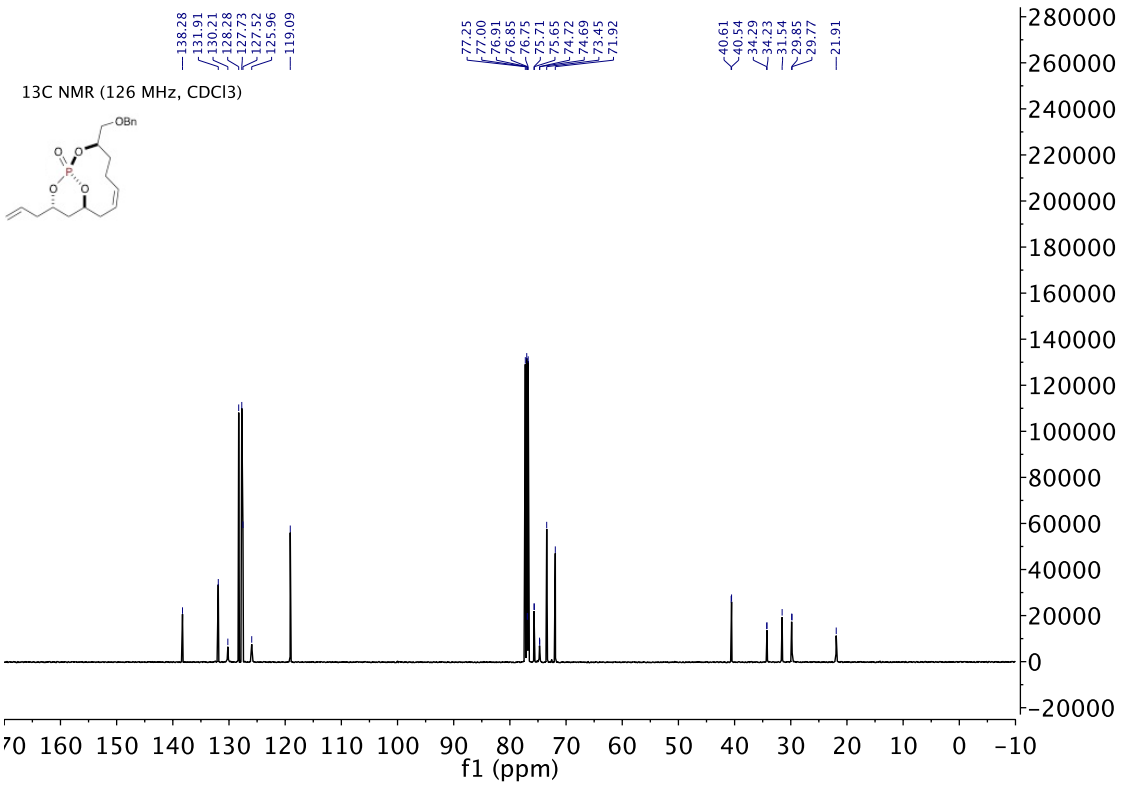

31P NMR (162 MHz, CDCl3)
OBn
7.18
1800
1600
1400
1200
1000
800
600
400
200
0
-200
40 120 100 80 60 40 20 0 -20 -40 -60 -80 -100 -120
f1 (ppm)

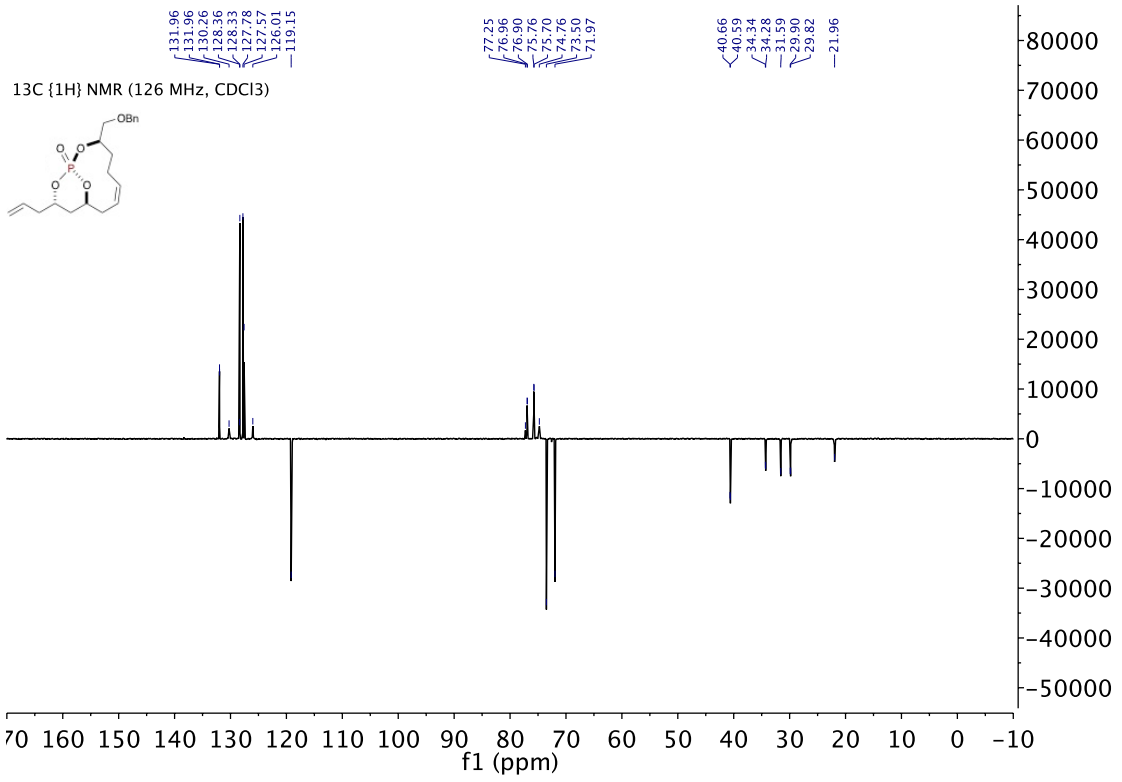

COSY (CDCl3)
OBn
0
1
2
3
4
5
6
7
8
9
10
11
12
f1 (ppm)
12 11 10 9 8 7 6 5 4 3 2 1 0
f2 (ppm)

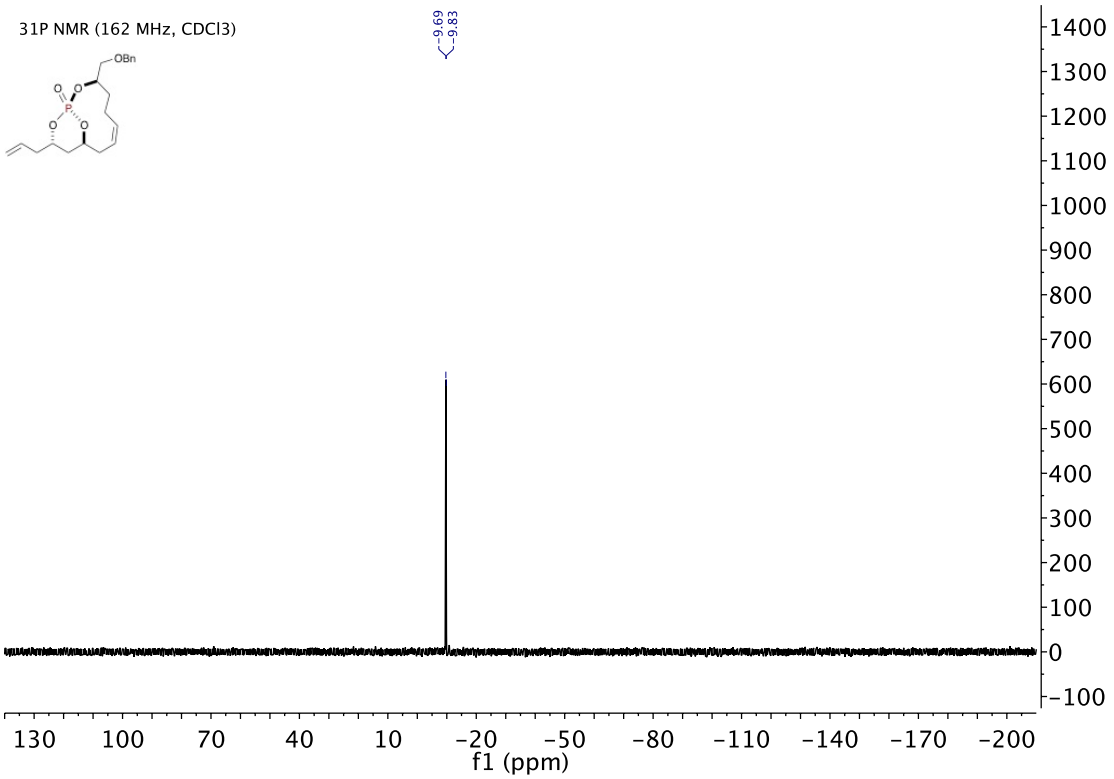

HSQC (CDCl3)
OBn
12 11 10 9 8 7 6 5 4 3 2 1 0 −1 −2 −3
f2 (ppm)
−10 10 30 50 70 90 110 130 150
f1 (ppm)

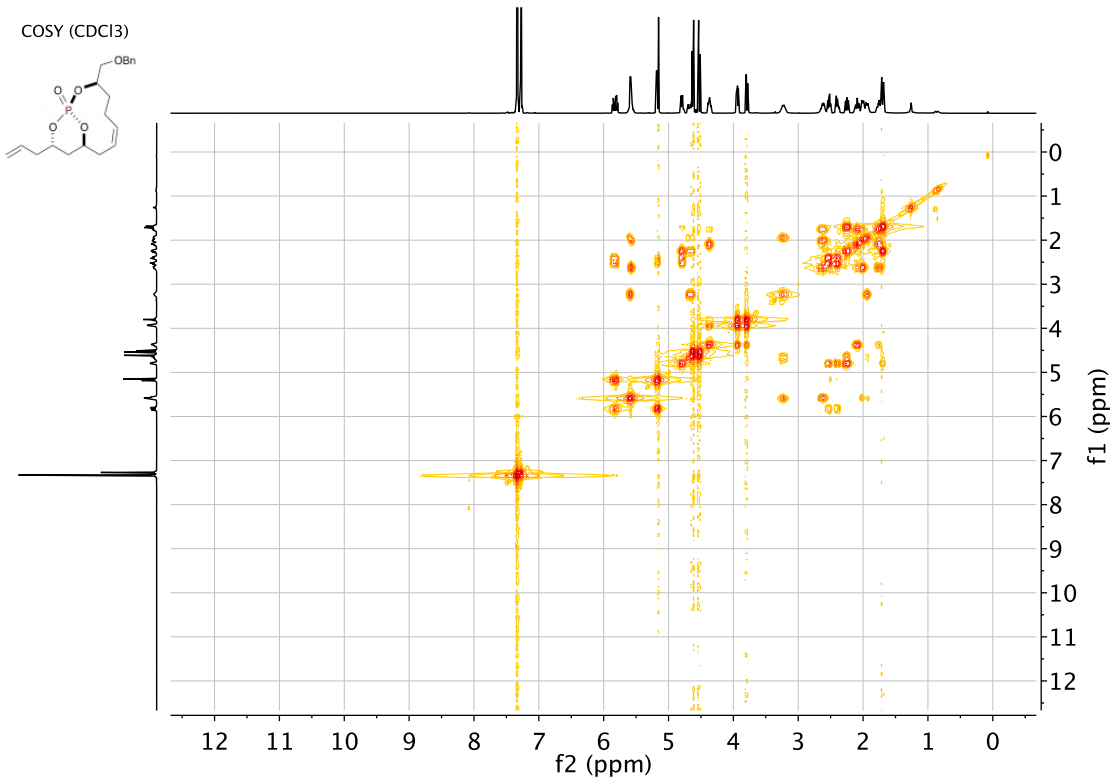
**(1*R*,3*R*,9*S*,11*S*,*Z*)-11-allyl-3-((benzyloxy)methyl)-2,12,13-trioxa-1-phosphabicyclo[7.3.1]tridec-6-ene 1-oxide (*cis*-2.12.6)**

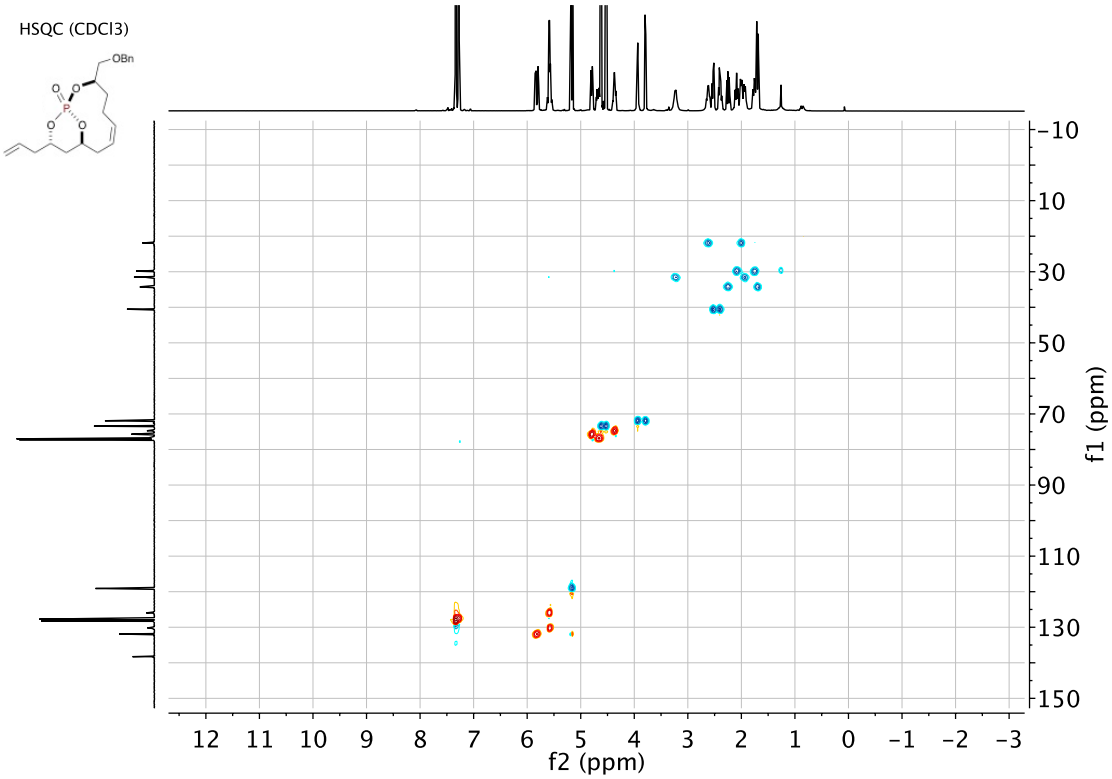


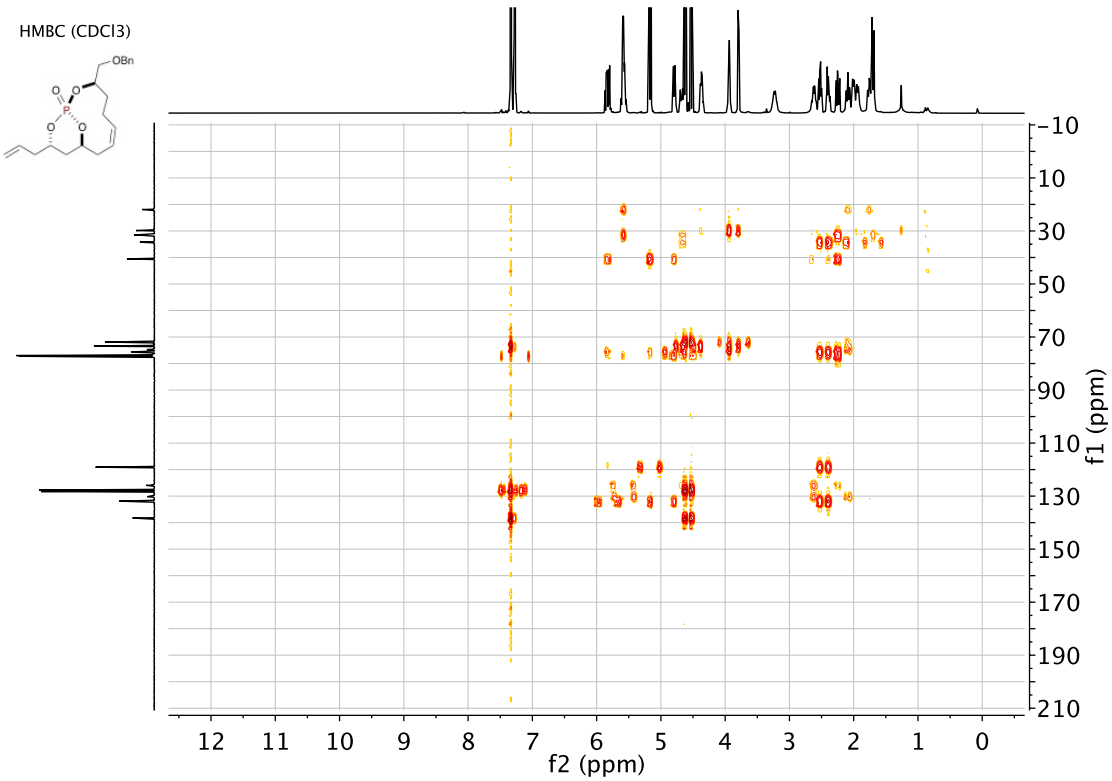

138.28
131.91
130.21
128.28
127.73
127.52
125.96
119.09
77.25
77.00
76.91
76.85
76.75
75.71
75.65
74.72
74.69
73.45
71.92
40.61
40.54
34.29
34.23
31.54
29.85
29.77
21.91
13C NMR (126 MHz, CDCl3)
OBn
f1 (ppm)

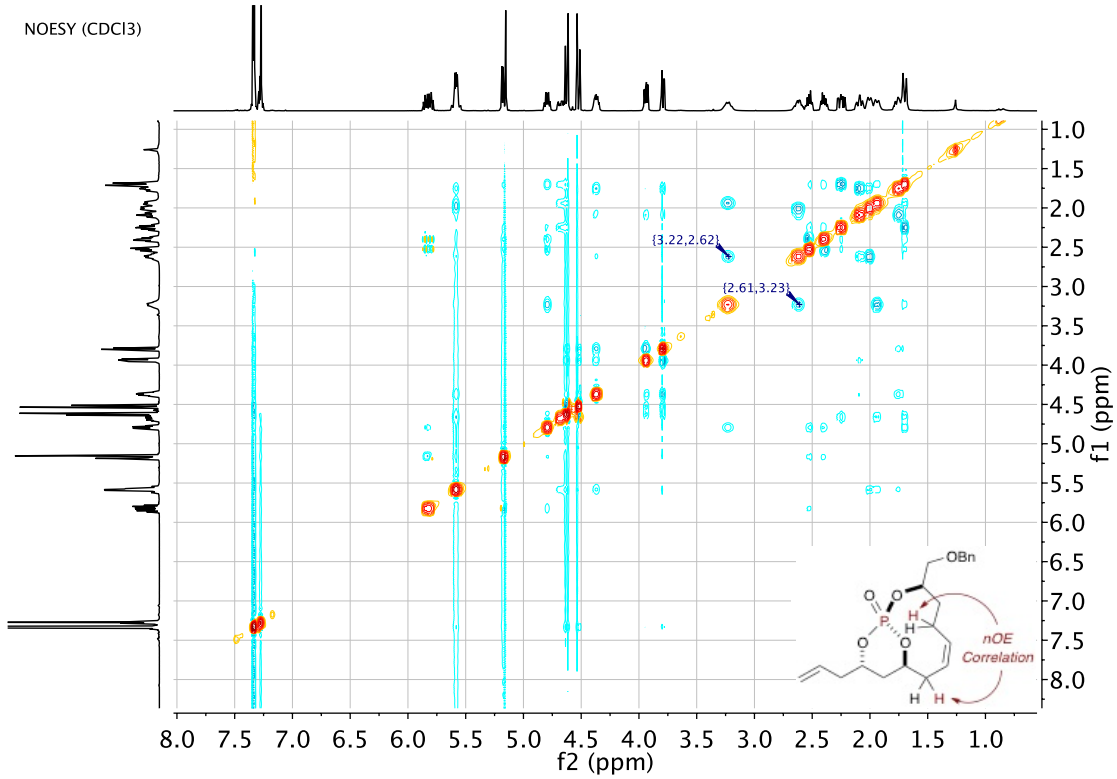

131.96
131.96
130.26
128.36
128.33
127.78
127.57
126.01
119.15
77.25
76.96
76.90
75.76
75.70
74.76
73.50
71.97
40.66
40.59
34.34
34.28
31.59
29.90
29.82
21.96
13C {1H} NMR (126 MHz, CDCl3)
OBn
f1 (ppm)


31P NMR (162 MHz, CDCl3)
OBn
9.69
9.83
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−100
130
100
70
40
10
−20
−50
−80
−110
−140
−170
−200
f1 (ppm)

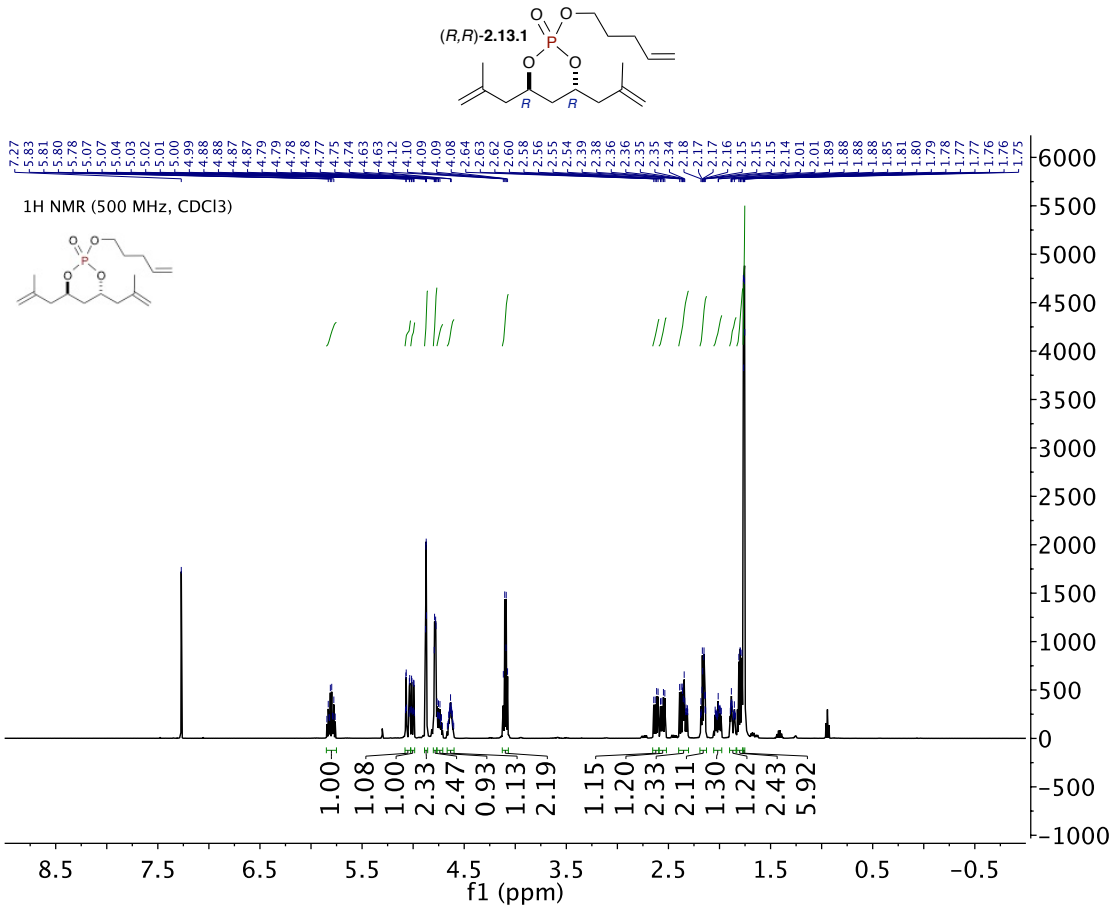

COSY (CDCl3)
OBn
0
1
2
3
4
5
6
7
8
9
10
11
12
f1 (ppm)
12
11
10
9
8
7
6
5
4
3
2
1
0
f2 (ppm)

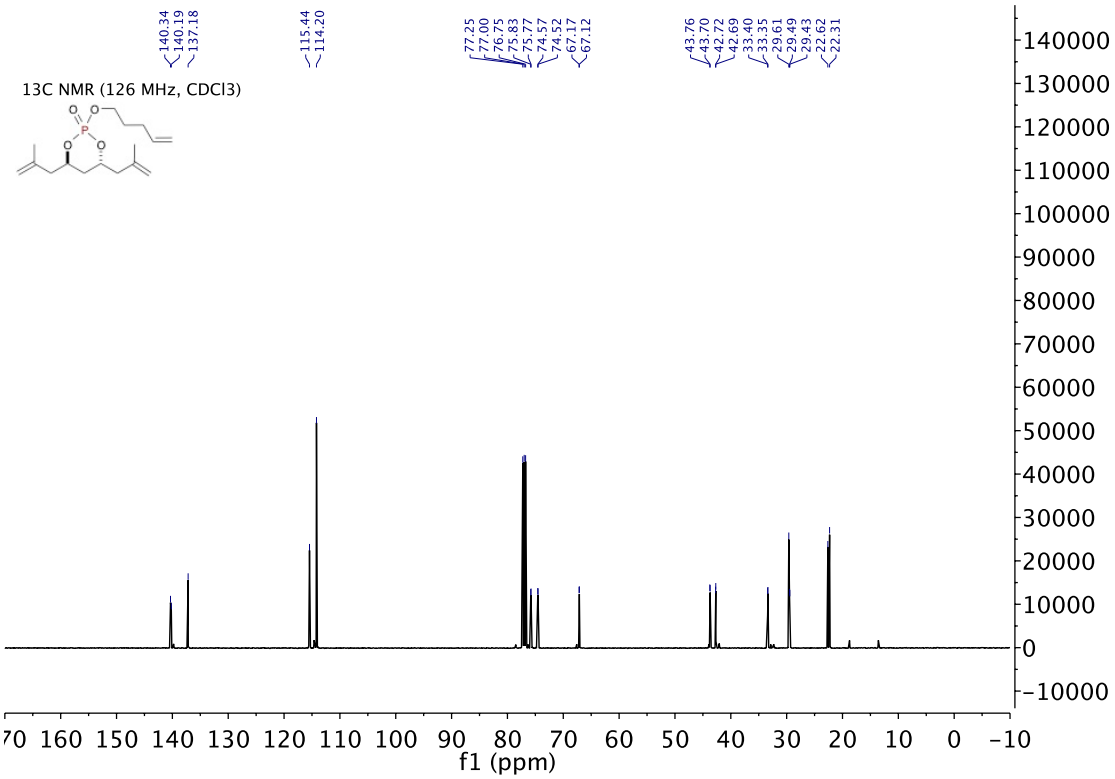

HSQC (CDCl3)
OBn
f2 (ppm)
f1 (ppm)

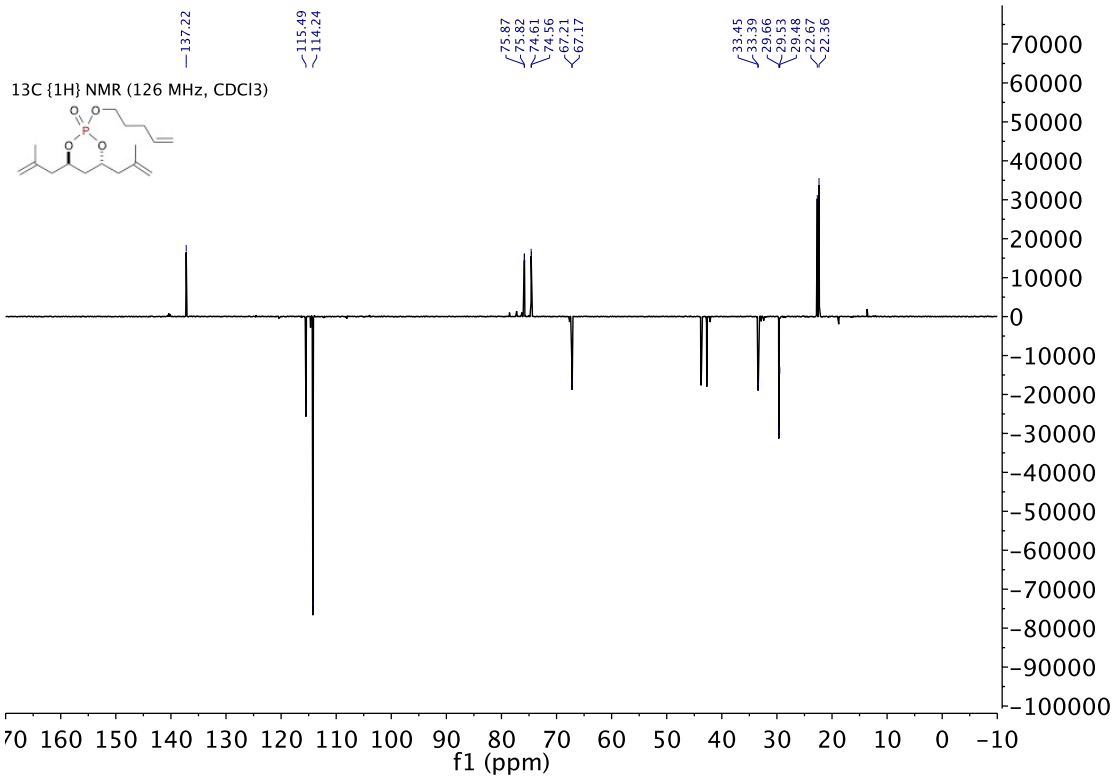

HMBC (CDCl3)
OBn
f2 (ppm)
f1 (ppm)

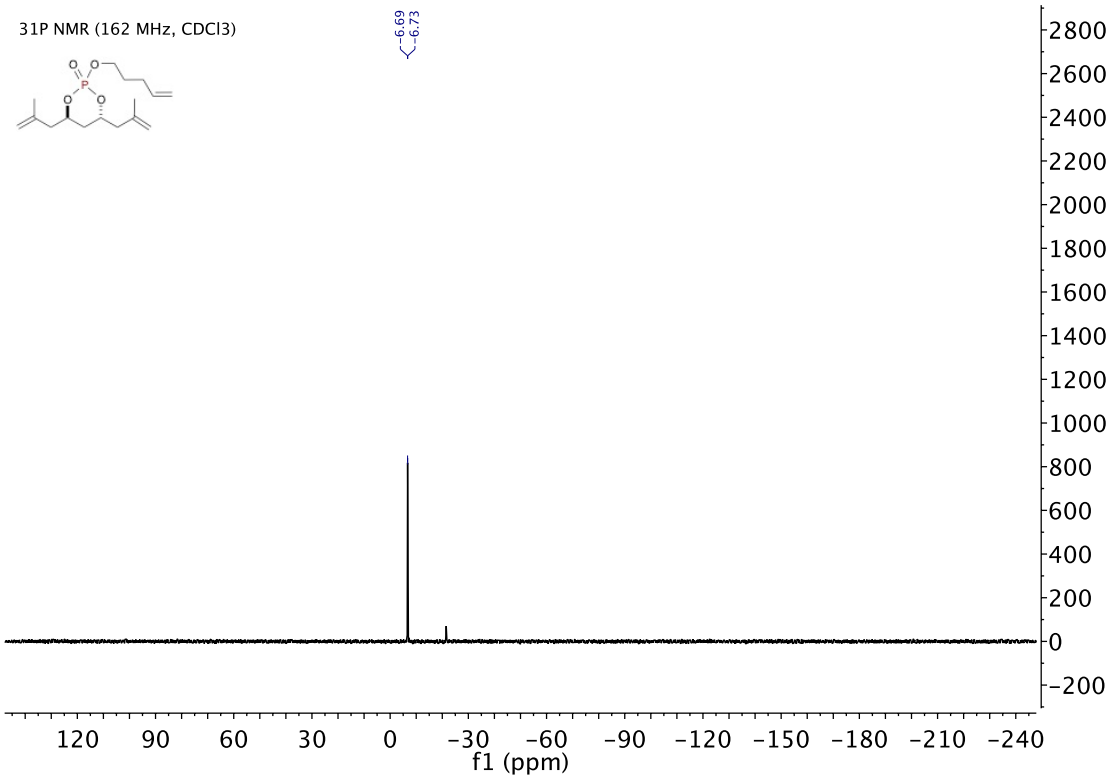

NOESY (CDCl3)
{3.22,2.62}
{2.61,3.23}
OBn
nOE
Correlation
f1 (ppm)
f2 (ppm)

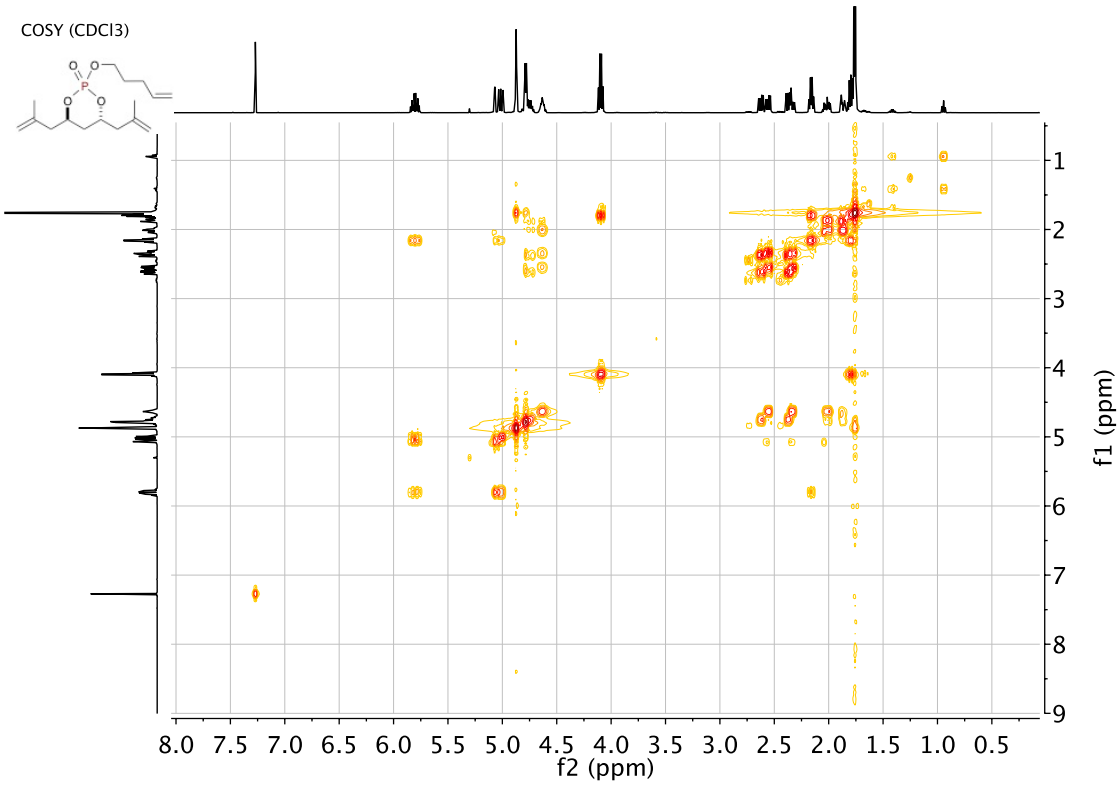
**(4*R*,6*R*)-4,6-bis(2-methylallyl)-2-(pent-4-en-1-yloxy)-1,3,2-dioxaphosphinane 2-oxide (2.13.1)**

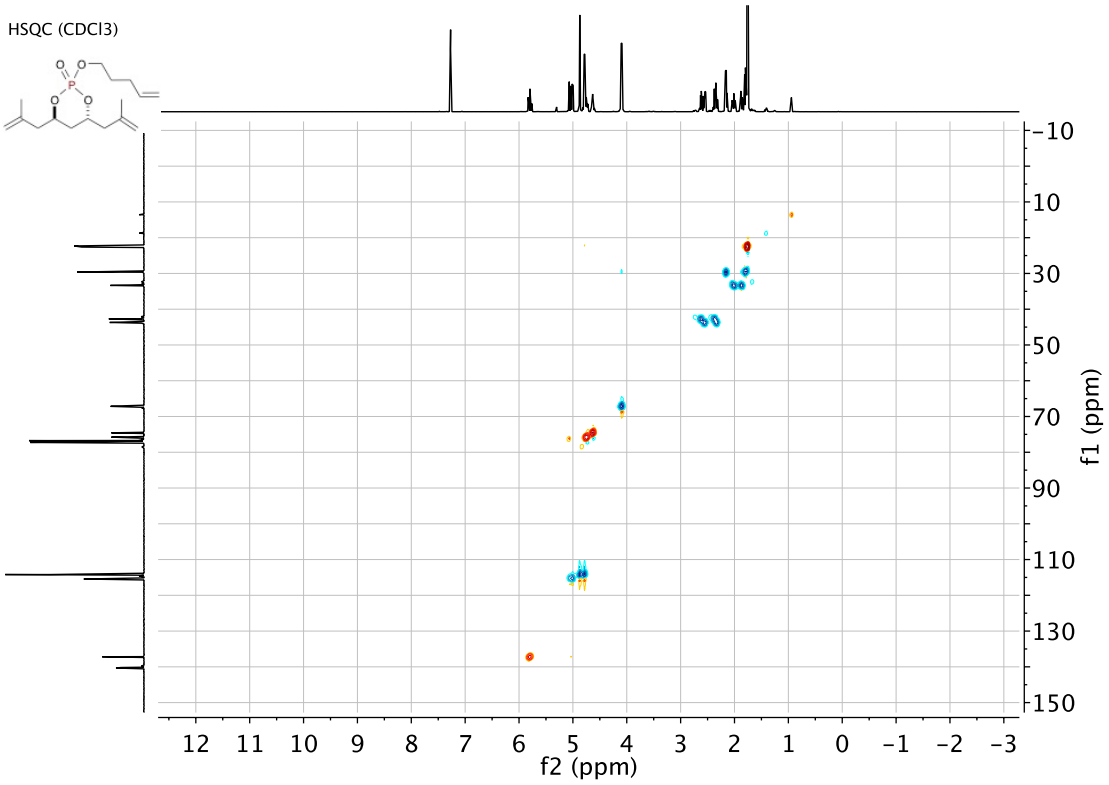



140.34
140.19
137.18
115.44
114.20
77.25
77.00
76.75
75.83
75.77
74.57
74.52
67.17
67.12
43.76
43.70
42.72
42.69
33.40
33.35
29.61
29.49
29.43
22.62
22.31
13C NMR (126 MHz, CDCl3)
f1 (ppm)

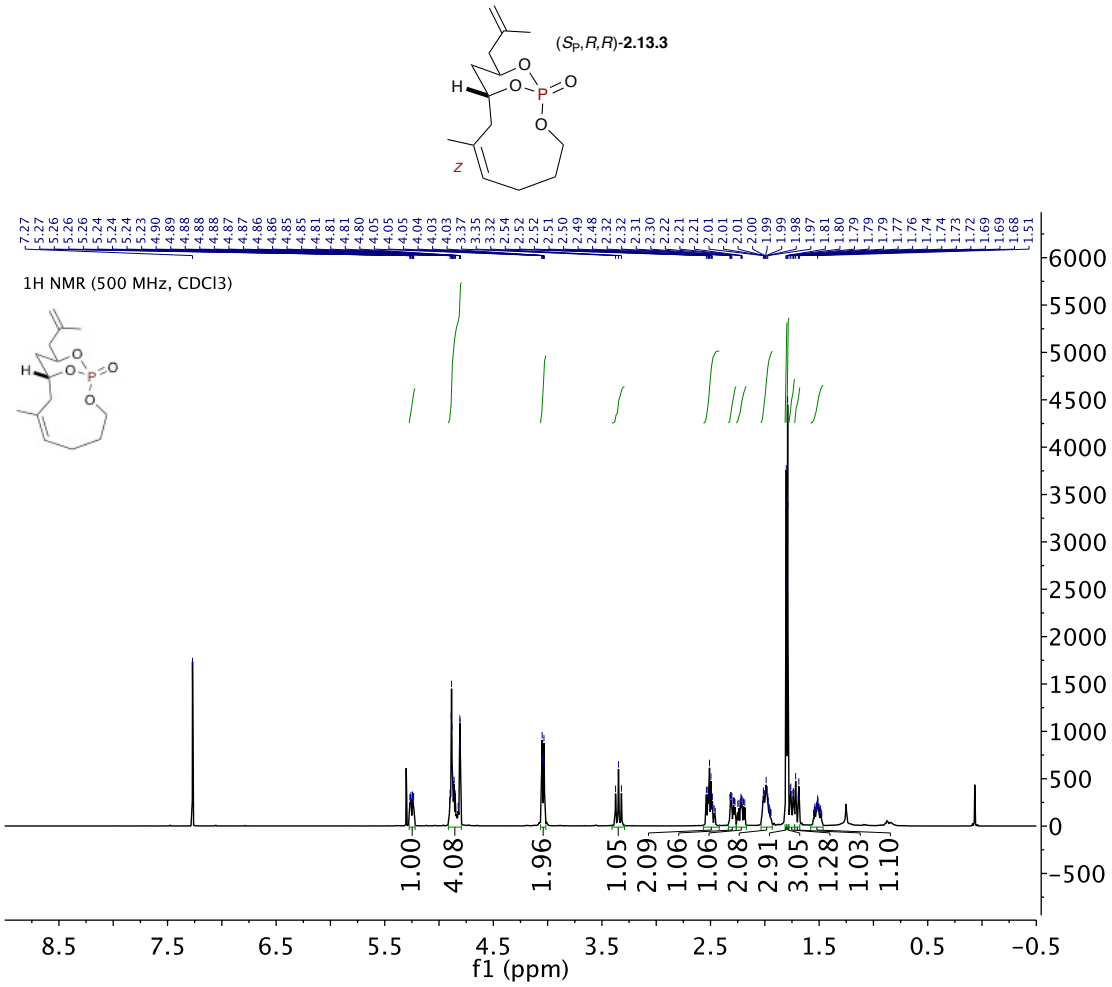

137.22
115.49
114.24
75.87
75.82
74.61
74.56
67.21
67.17
33.45
33.39
29.66
29.53
29.48
22.67
22.36
13C {1H} NMR (126 MHz, CDCl3)
f1 (ppm)

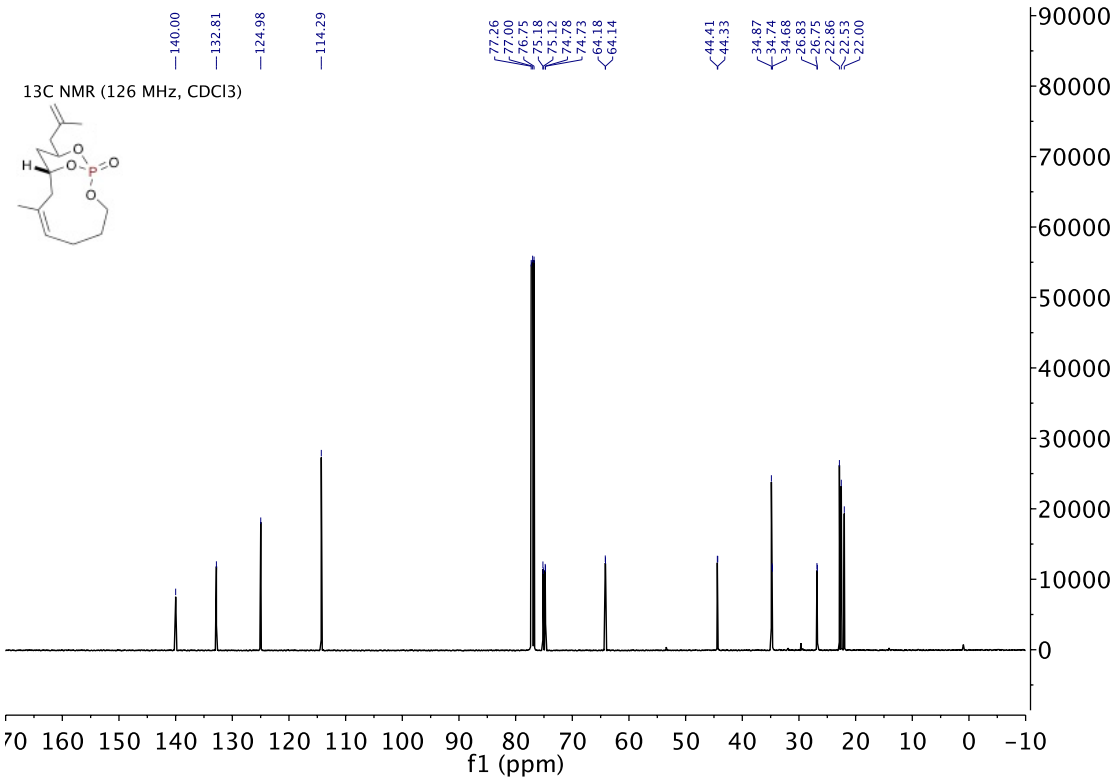

31P NMR (162 MHz, CDCl3)
6.69
6.73
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
−200
120 90 60 30 0 −30 −60 −90 −120 −150 −180 −210 −240
f1 (ppm)

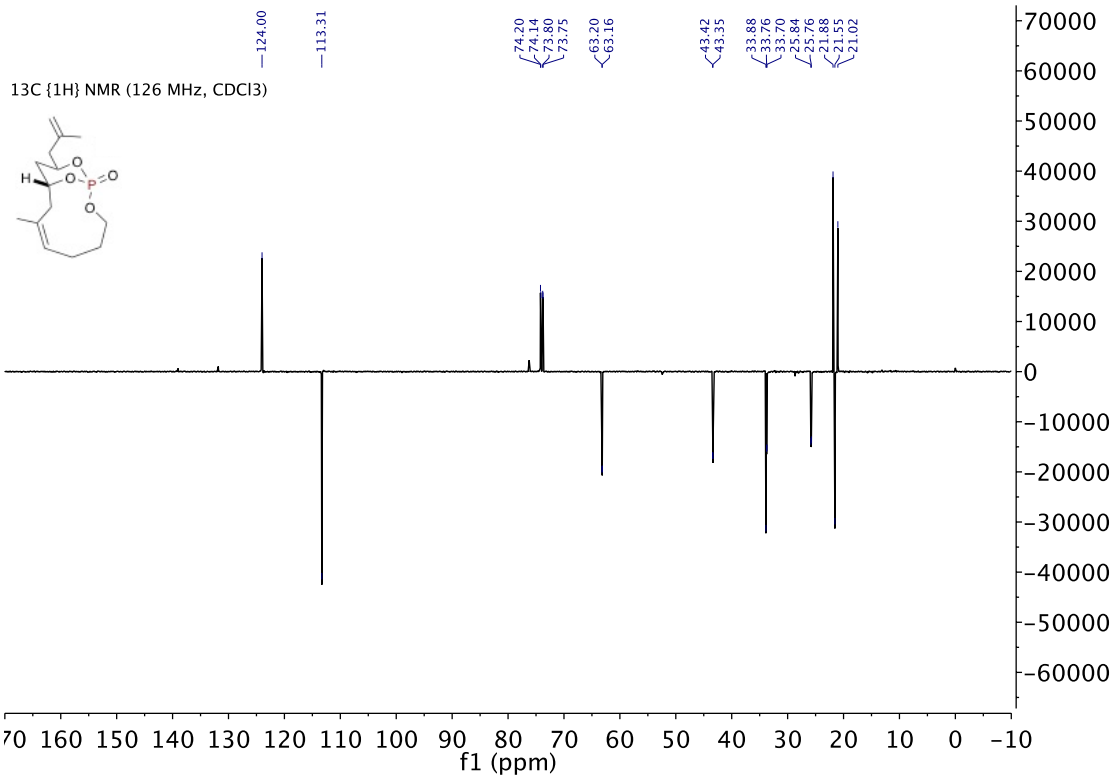

COSY (CDCl3)
1
2
3
4
5
6
7
8
9
f1 (ppm)
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f2 (ppm)

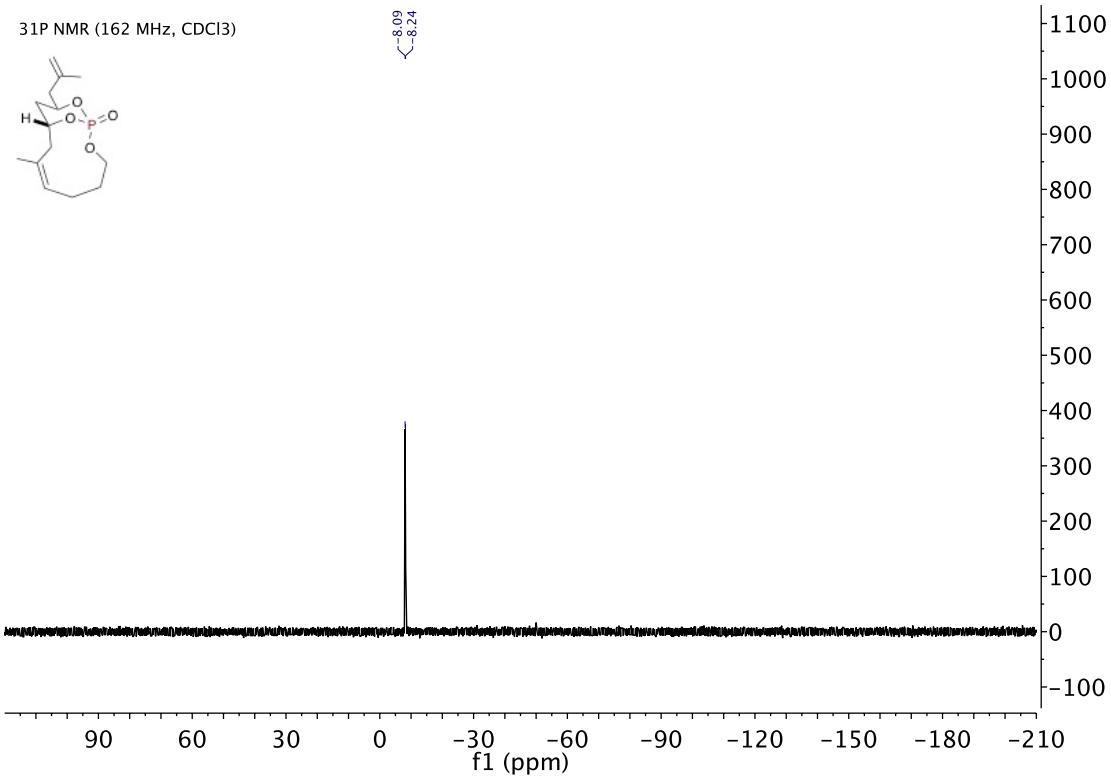

HSQC (CDCl3)
f2 (ppm)
f1 (ppm)
12
11
10
9
8
7
6
5
4
3
2
1
0
−1
−2
−3
−10
10
30
50
70
90
110
130
150

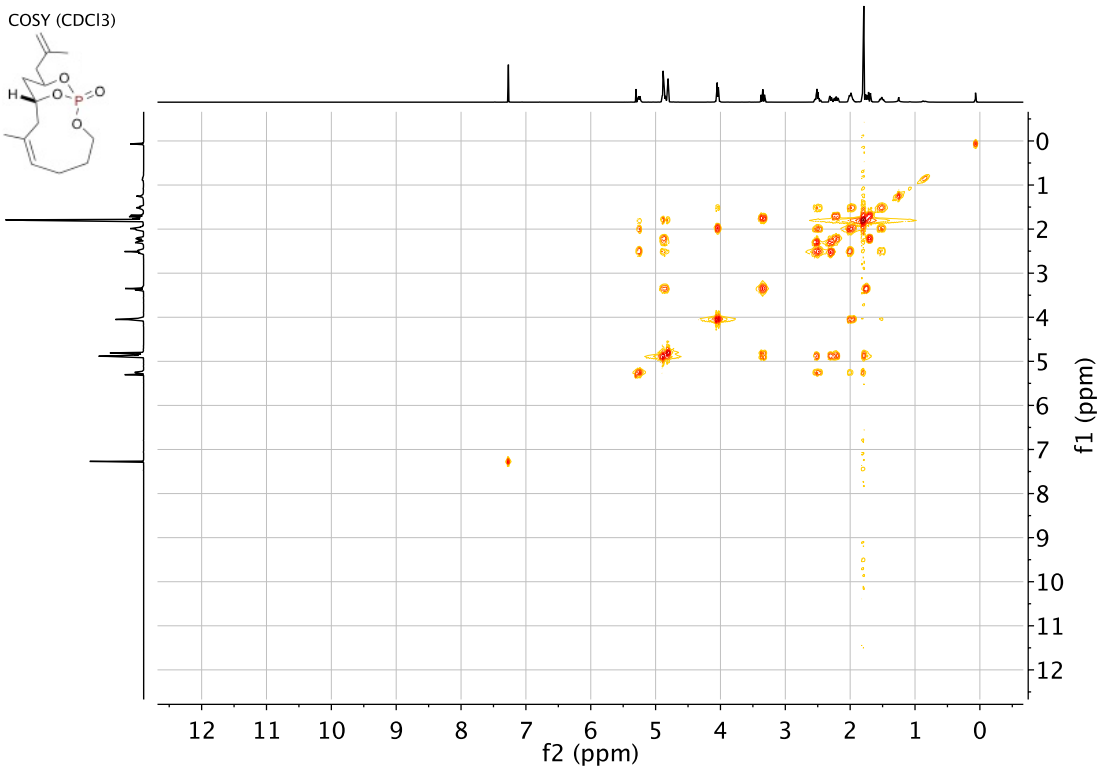
**(1*S*,9*R*,11*R*,*Z*)-7-methyl-11-(2-methylallyl)-2,12,13-trioxa-1-phosphabicyclo[7.3.1]tridec-6-ene 1-oxide (2.13.3)**

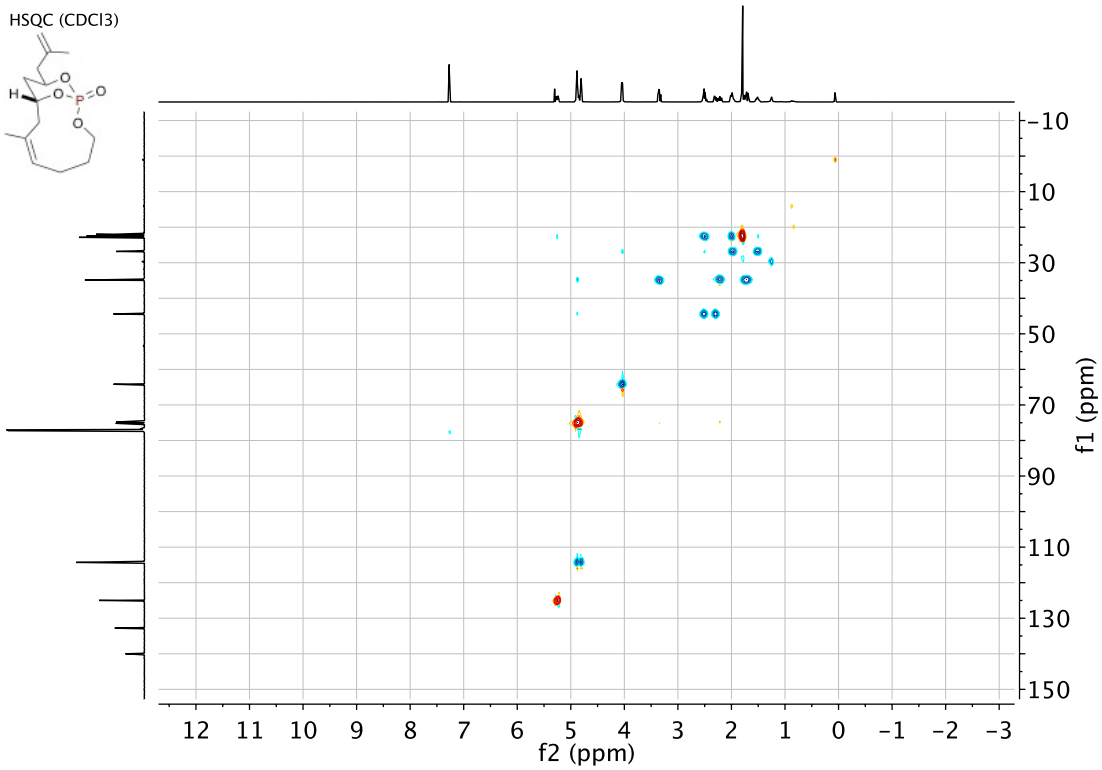


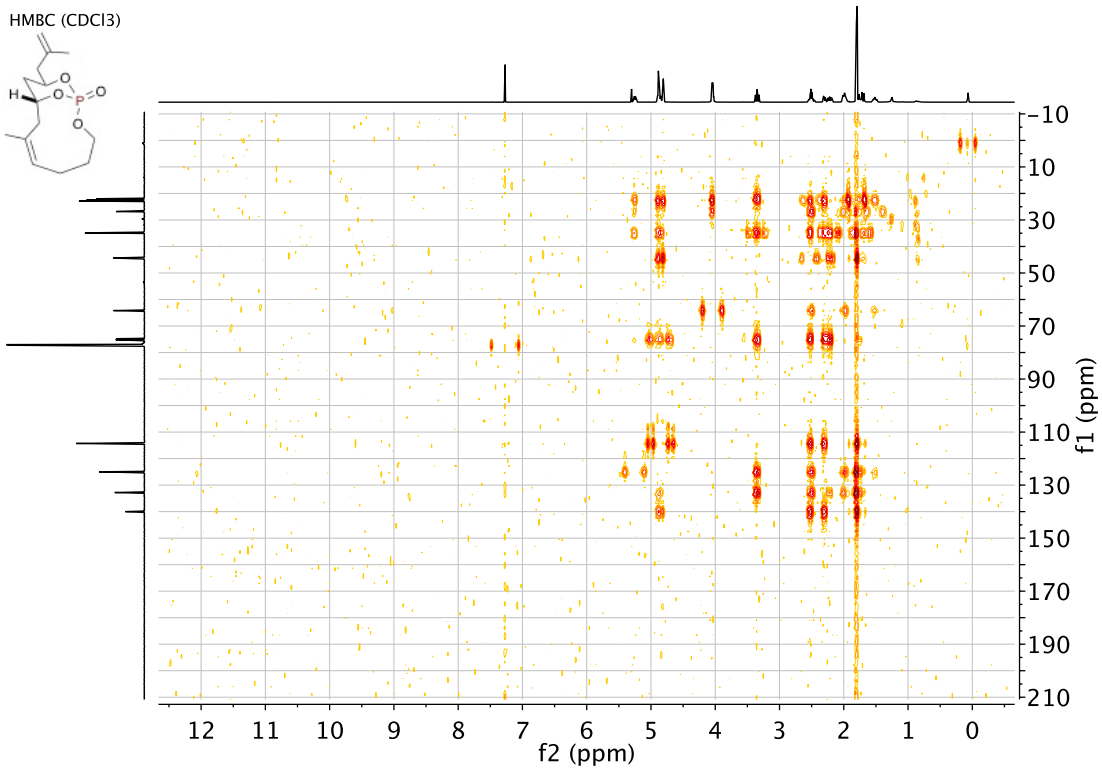

13C NMR (126 MHz, CDCl3)
140.00
132.81
124.98
114.29
77.26
77.00
76.75
75.18
75.12
74.78
74.73
64.18
64.14
44.41
44.33
34.87
34.74
34.68
26.83
26.75
22.86
22.53
22.00
f1 (ppm)

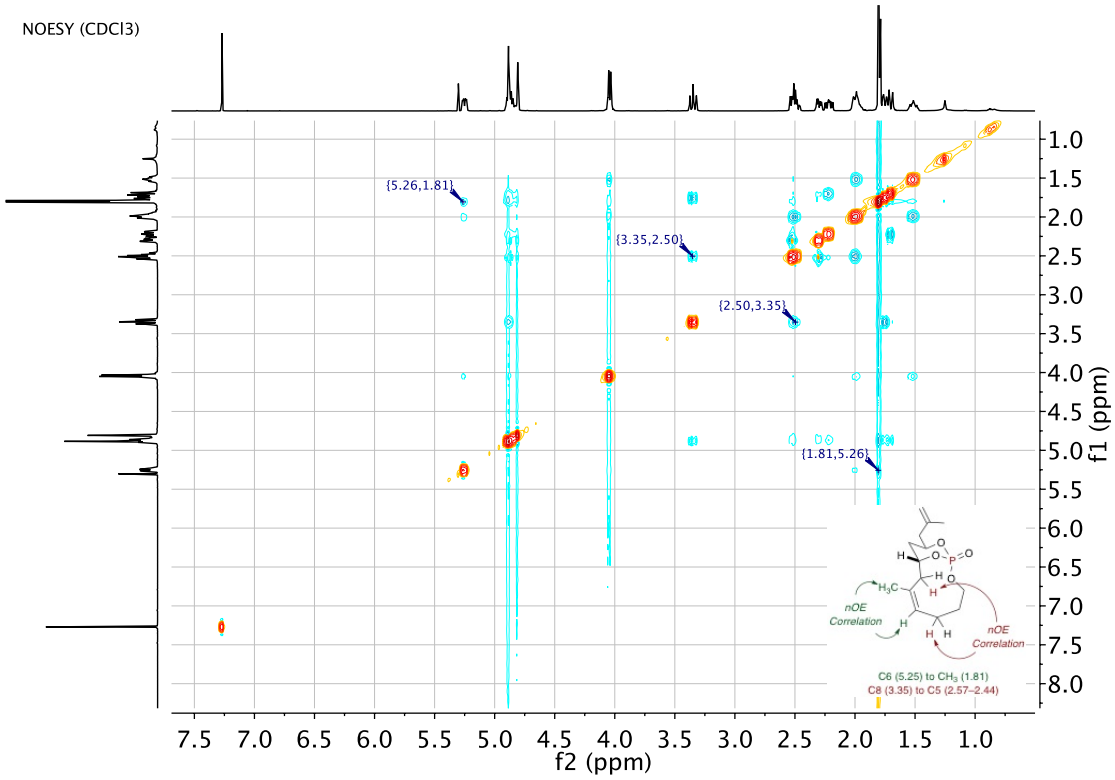

13C {1H} NMR (126 MHz, CDCl3)
124.00
113.31
74.20
74.14
73.80
73.75
63.20
63.16
43.42
43.35
33.88
33.76
33.70
25.84
25.76
21.88
21.55
21.02
f1 (ppm)


31P NMR (162 MHz, CDCl3)
8.09
8.24
1100
1000
900
800
700
600
500
400
300
200
100
0
−100
90
60
30
0
−30
−60
−90
−120
−150
−180
−210
f1 (ppm)

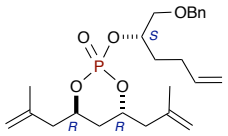

COSY (CDCl3)
0
1
2
3
4
5
6
7
8
9
10
11
12
f1 (ppm)
12
11
10
9
8
7
6
5
4
3
2
1
0
f2 (ppm)


HSQC (CDCl3)
f2 (ppm)
f1 (ppm)

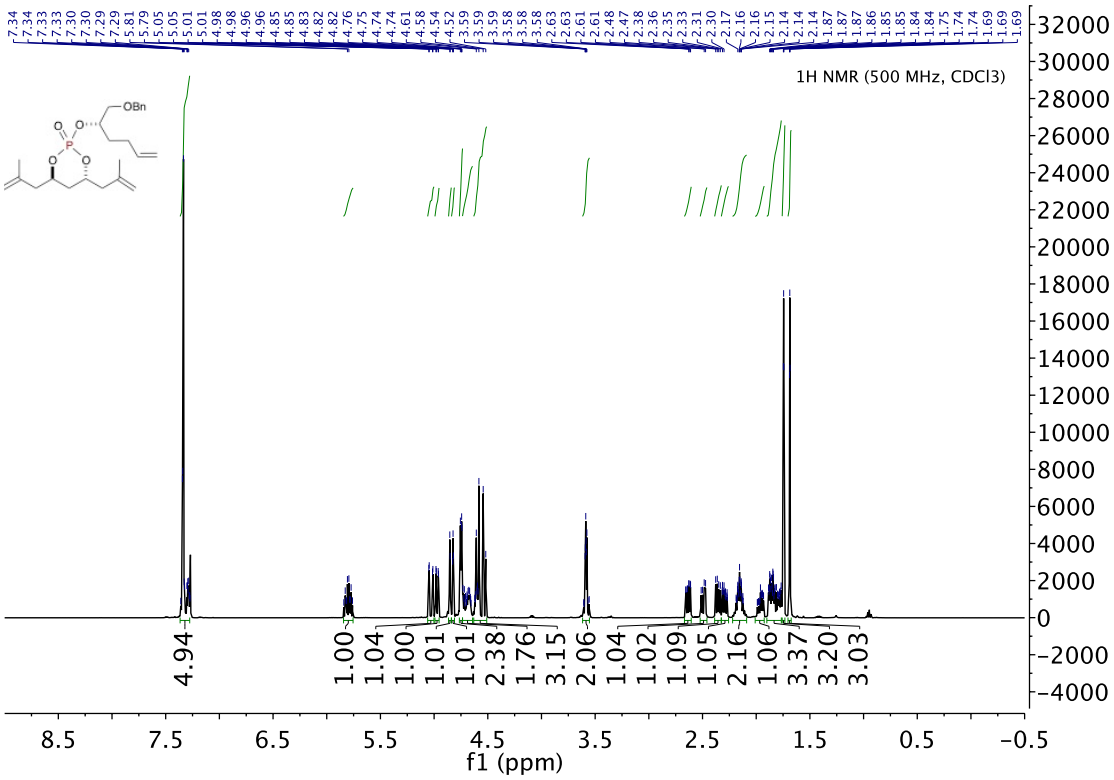

HMBC (CDCl3)
f2 (ppm)
f1 (ppm)

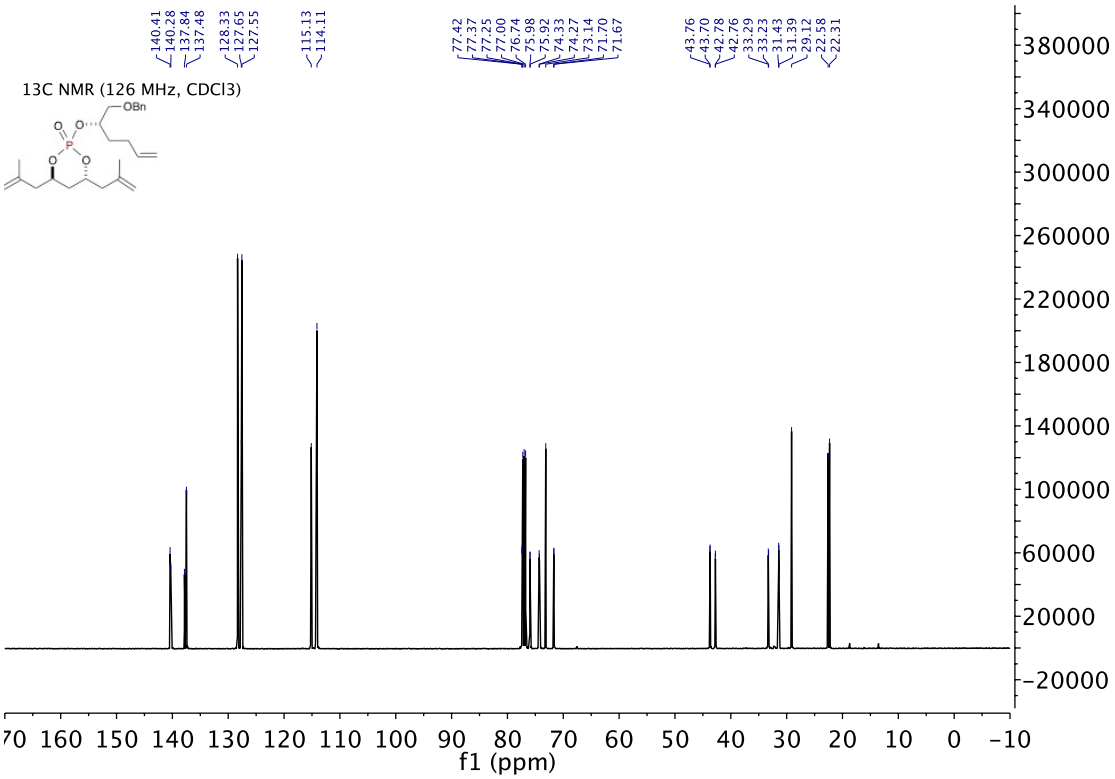

NOESY (CDCl3)
{5.26,1.81}
{3.35,2.50}
{2.50,3.35}
{1.81,5.26}
nOE Correlation
nOE Correlation
C6 (5.25) to CH3 (1.81)
C8 (3.35) to C5 (2.57–2.44)
f2 (ppm)
f1 (ppm)

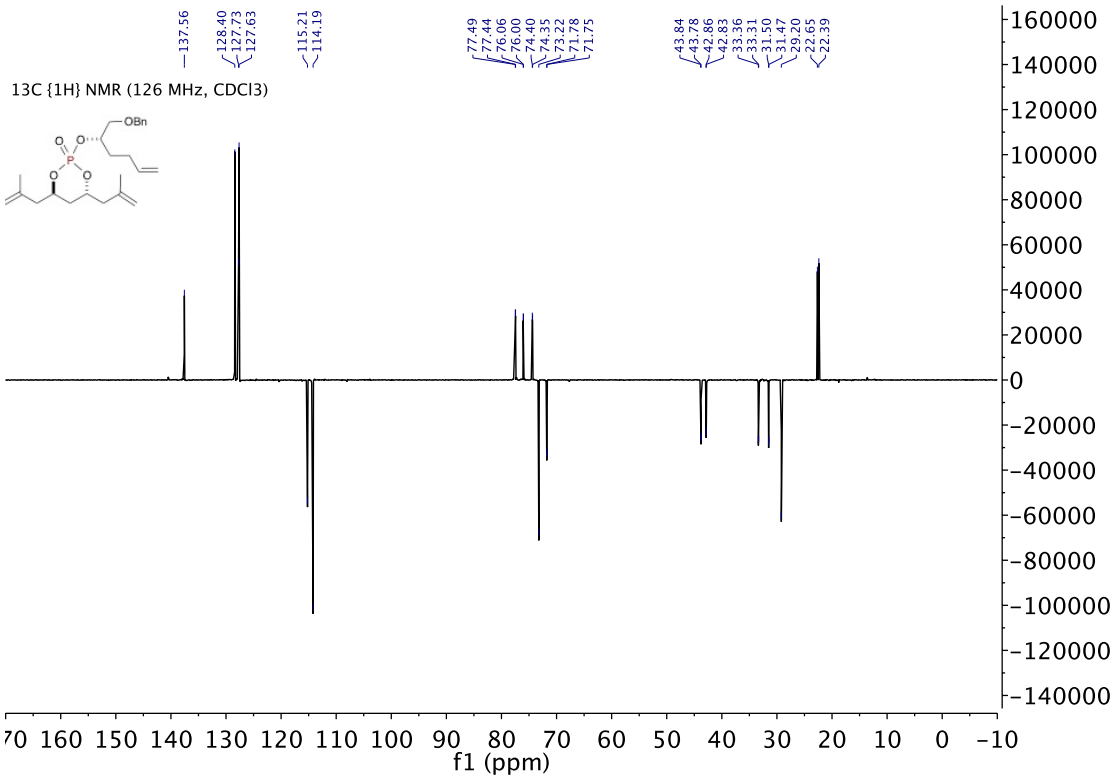
**(4*R*,6*R*)-2-(((*S*)-1-(benzyloxy)hex-5-en-2-yl)oxy)-4,6-bis(2-methylallyl)-1,3,2-dioxaphosphinane 2-oxide (2.13.4)**

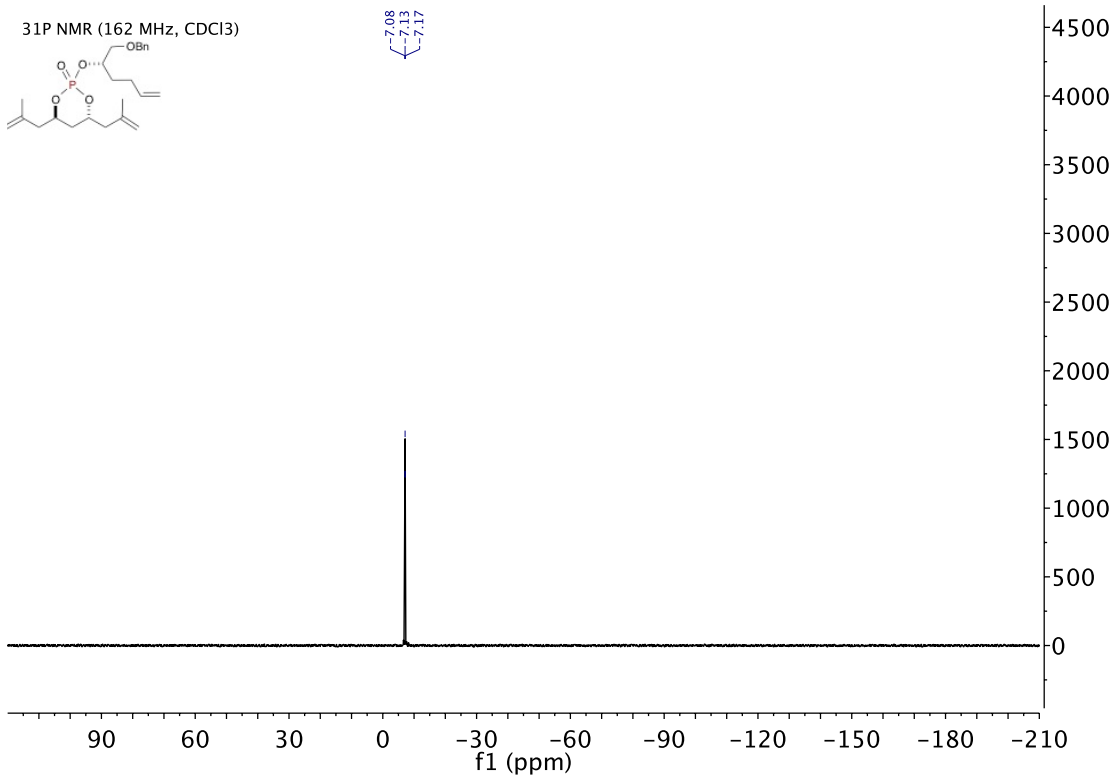


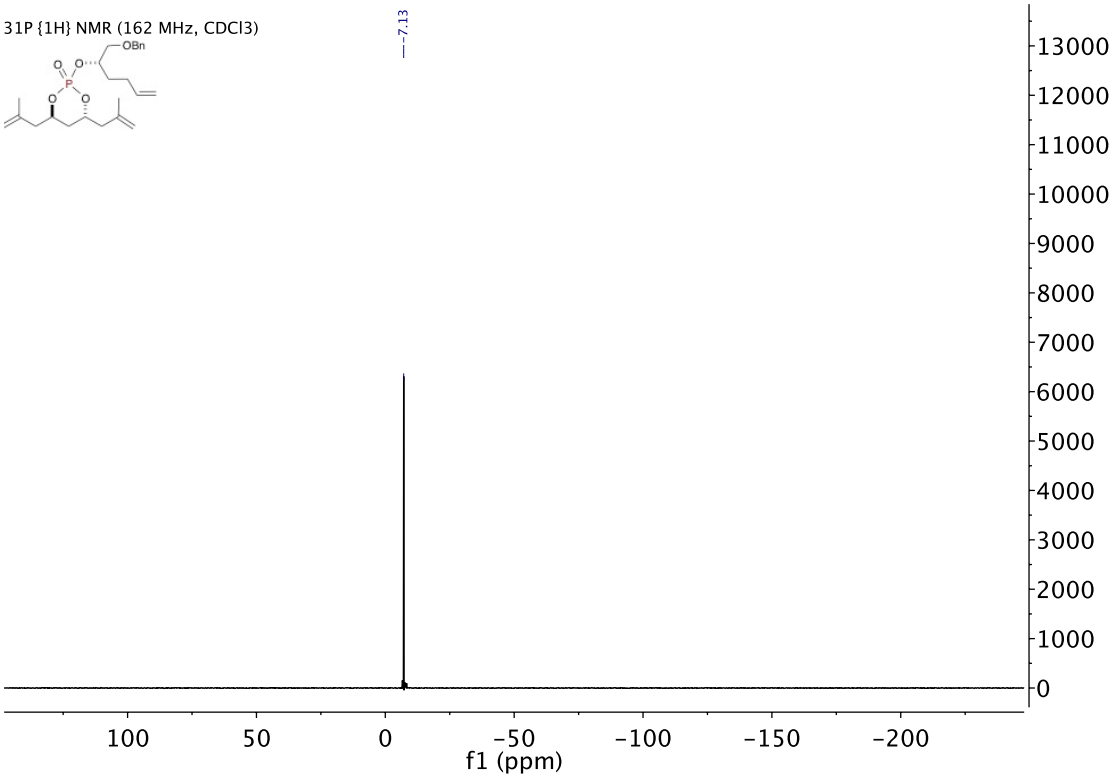

(*R*,*R*,*S*)-**2.13.4**

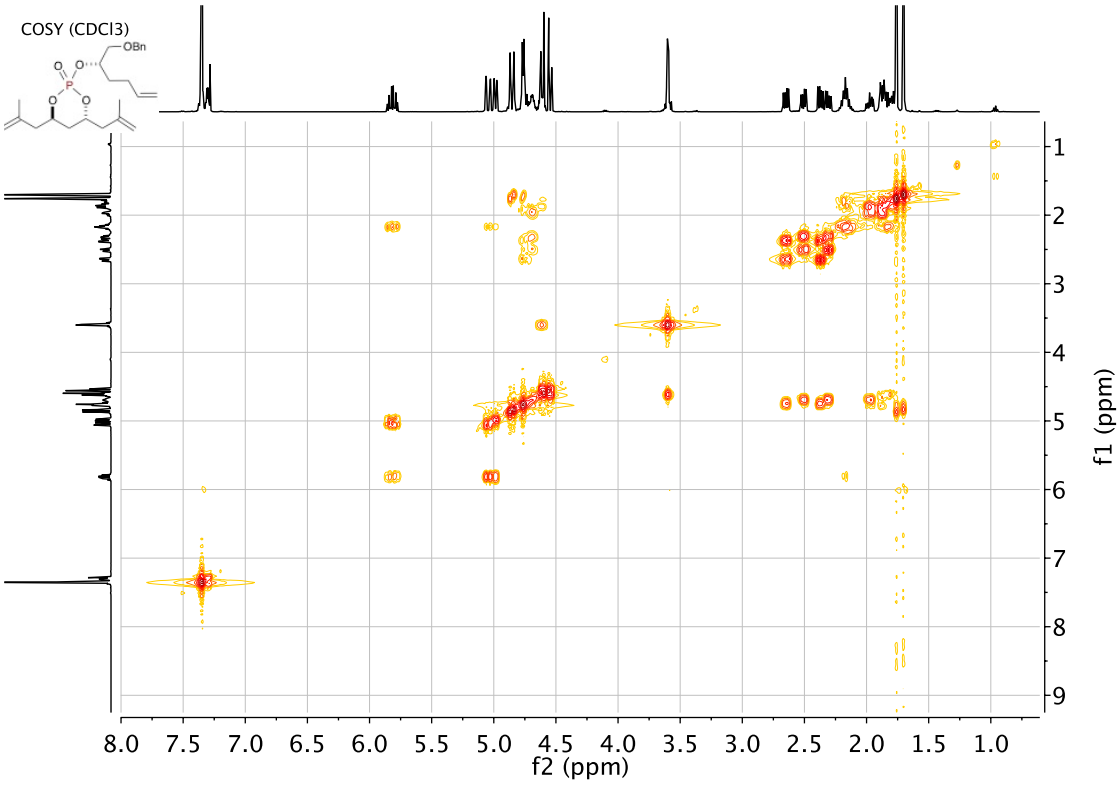


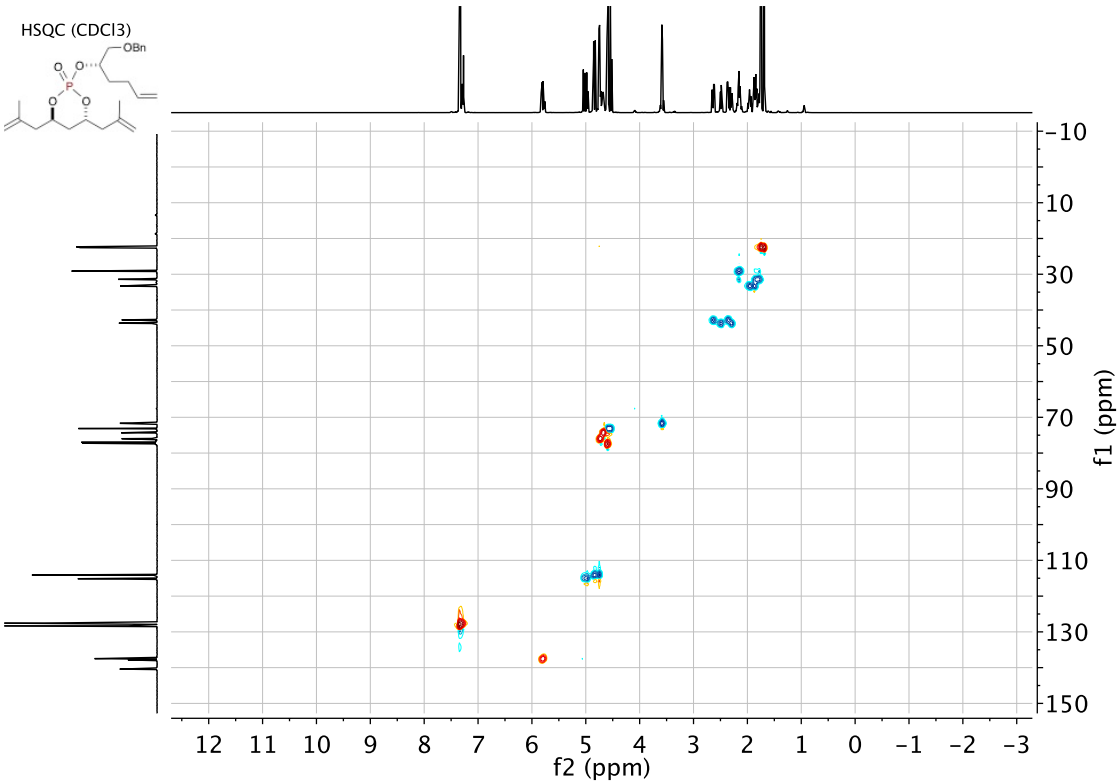

140.41
140.28
137.84
137.48
128.33
127.65
127.55
115.13
114.11
77.42
77.37
77.25
77.00
76.74
75.98
75.92
74.33
74.27
73.14
71.70
71.67
43.76
43.70
42.78
42.76
33.29
33.23
31.43
31.39
29.12
22.58
22.31
13C NMR (126 MHz, CDCl3)
OBn
380000
340000
300000
260000
220000
180000
140000
100000
60000
20000
-20000
70 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


137.56
128.40
127.73
127.63
115.21
114.19
77.49
77.44
76.06
76.00
74.40
74.35
73.22
71.78
71.75
43.84
43.78
42.86
42.83
33.36
33.31
31.50
31.47
29.20
22.65
22.39
13C {1H} NMR (126 MHz, CDCl3)
OBn
160000
140000
120000
100000
80000
60000
40000
20000
0
-20000
-40000
-60000
-80000
-100000
-120000
-140000
70 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

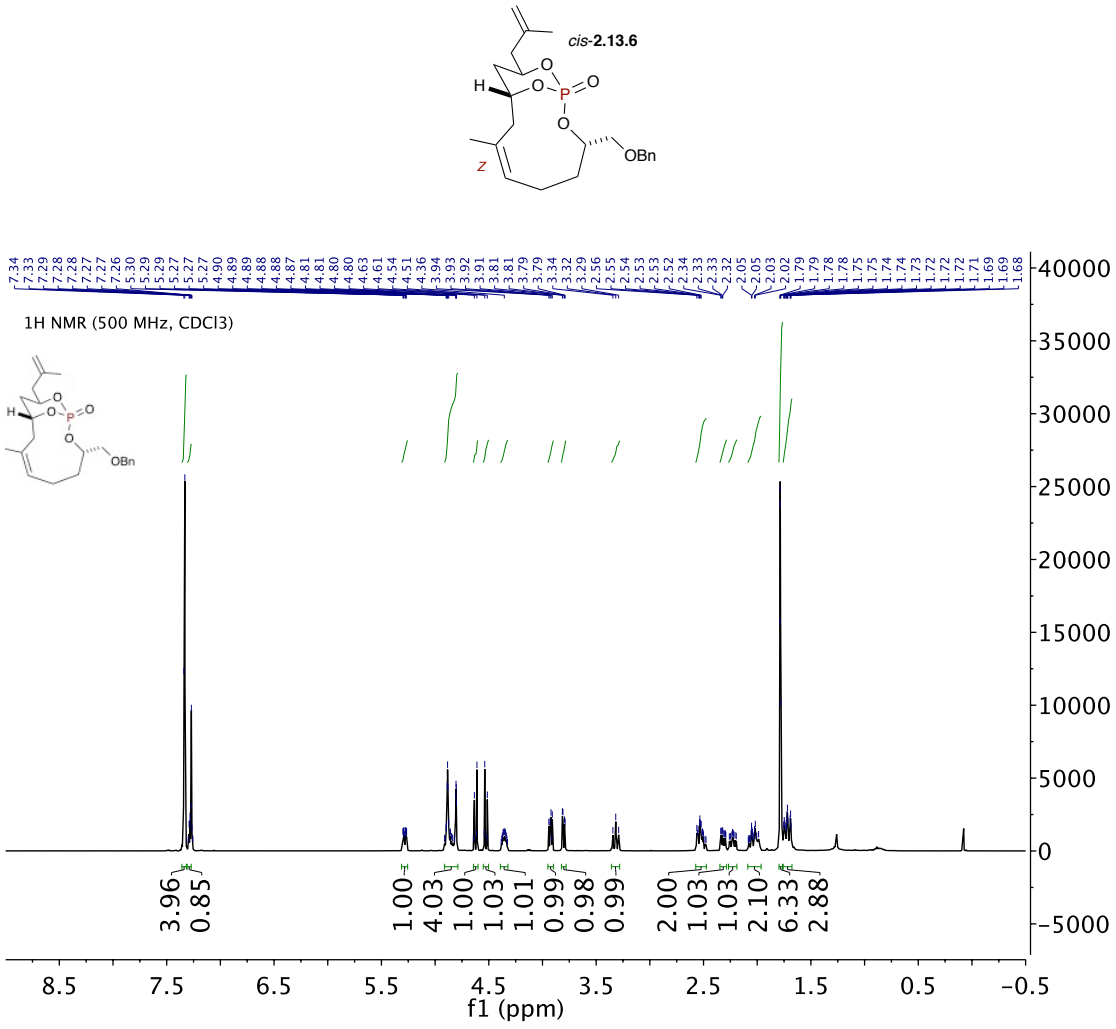

31P NMR (162 MHz, CDCl3)
OBn
7.08
7.13
7.17
4500
4000
3500
3000
2500
2000
1500
1000
500
0
90
60
30
0
−30
−60
−90
−120
−150
−180
−210
f1 (ppm)

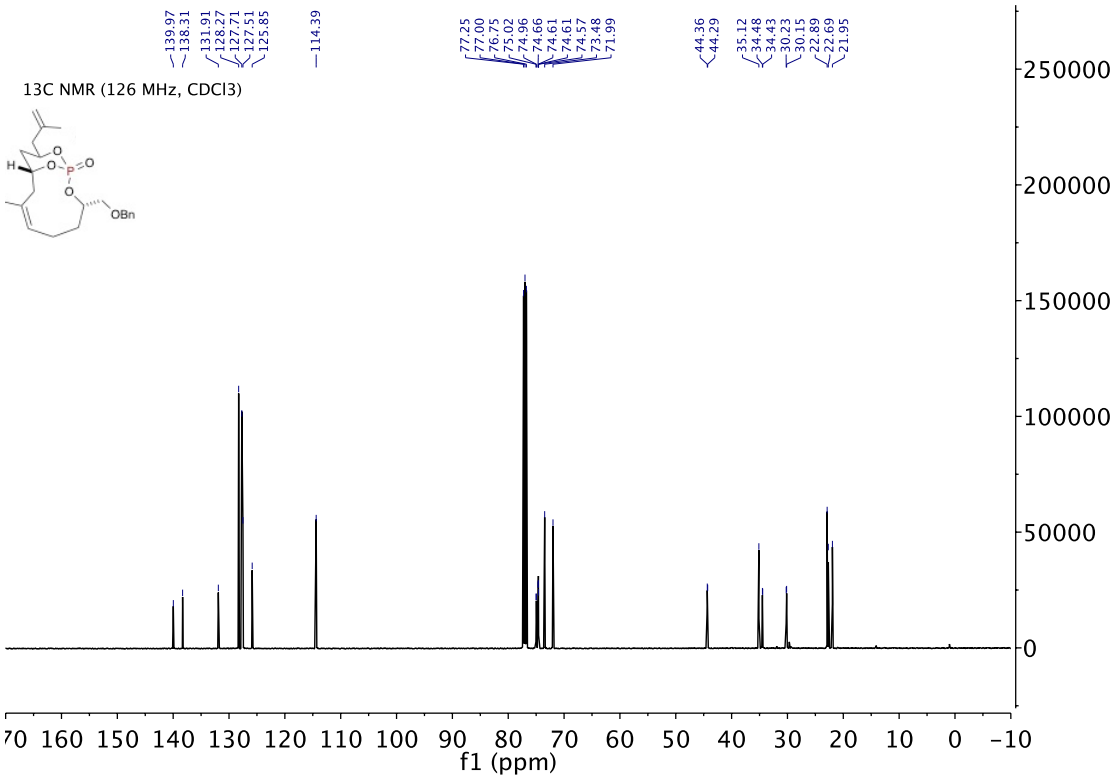

31P {1H} NMR (162 MHz, CDCl3)
OBn
7.13
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
100
50
0
−50
−100
−150
−200
f1 (ppm)

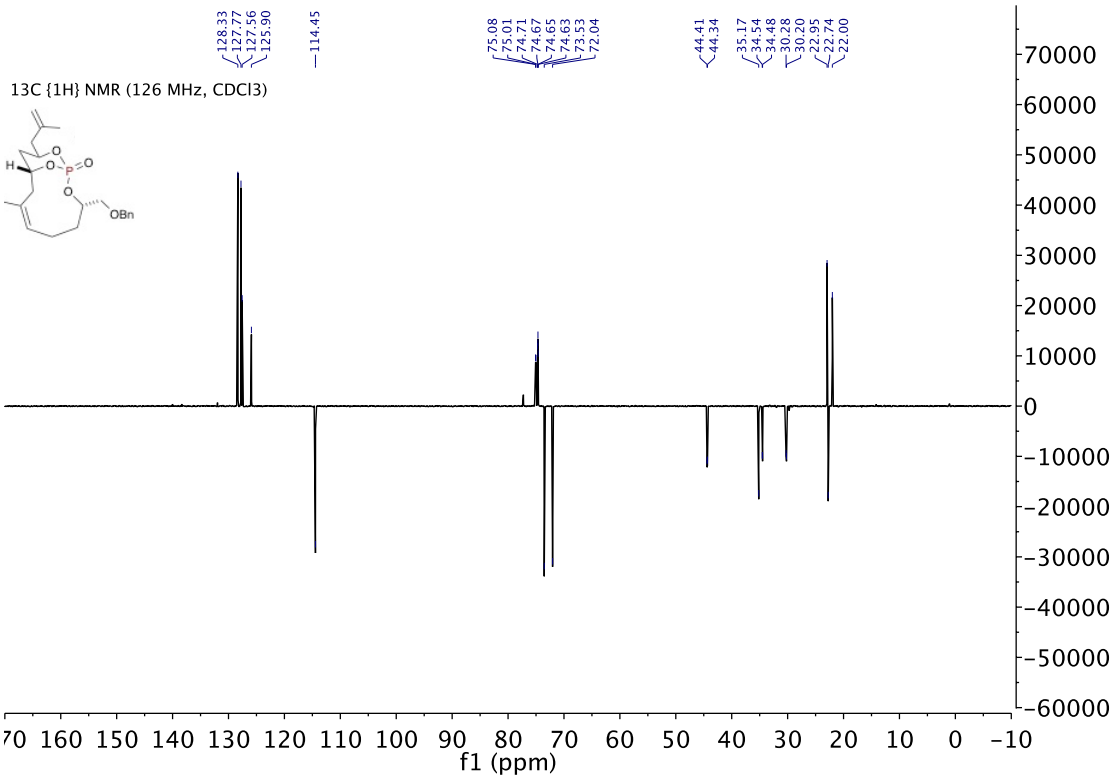

COSY (CDCl3)
OBn
f2 (ppm)
f1 (ppm)

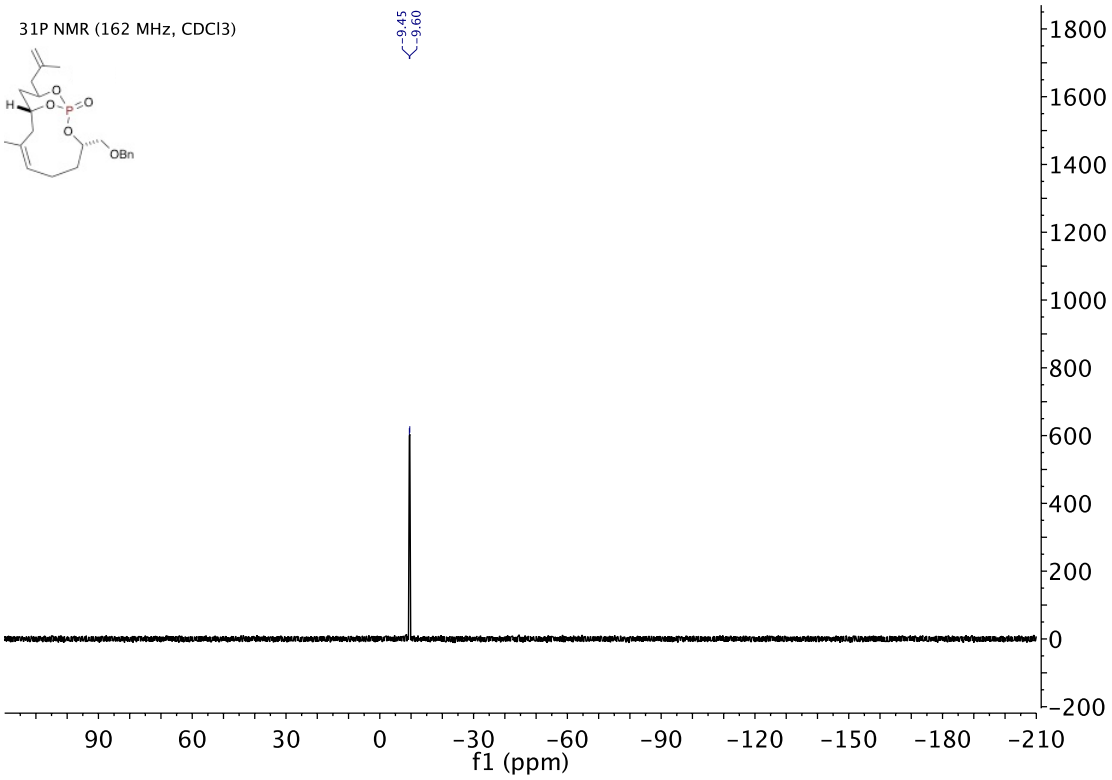

HSQC (CDCl3)
OBn
f2 (ppm)
f1 (ppm)

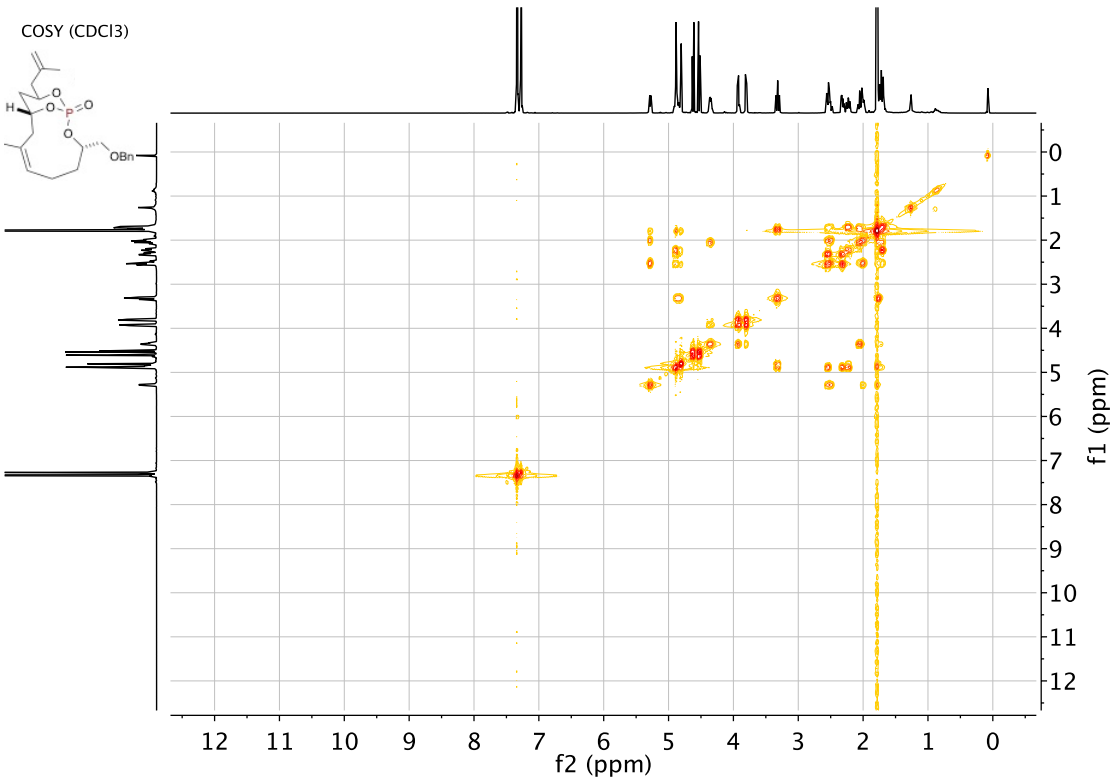
**(1*S*,3*S*,9*R*,11*R*,*Z*)-3-((benzyloxy)methyl)-7-methyl-11-(2-methylallyl)-2,12,13-trioxa-1-phosphabicyclo[7.3.1]tridec-6-ene 1-oxide (*cis*-2.13.6)**

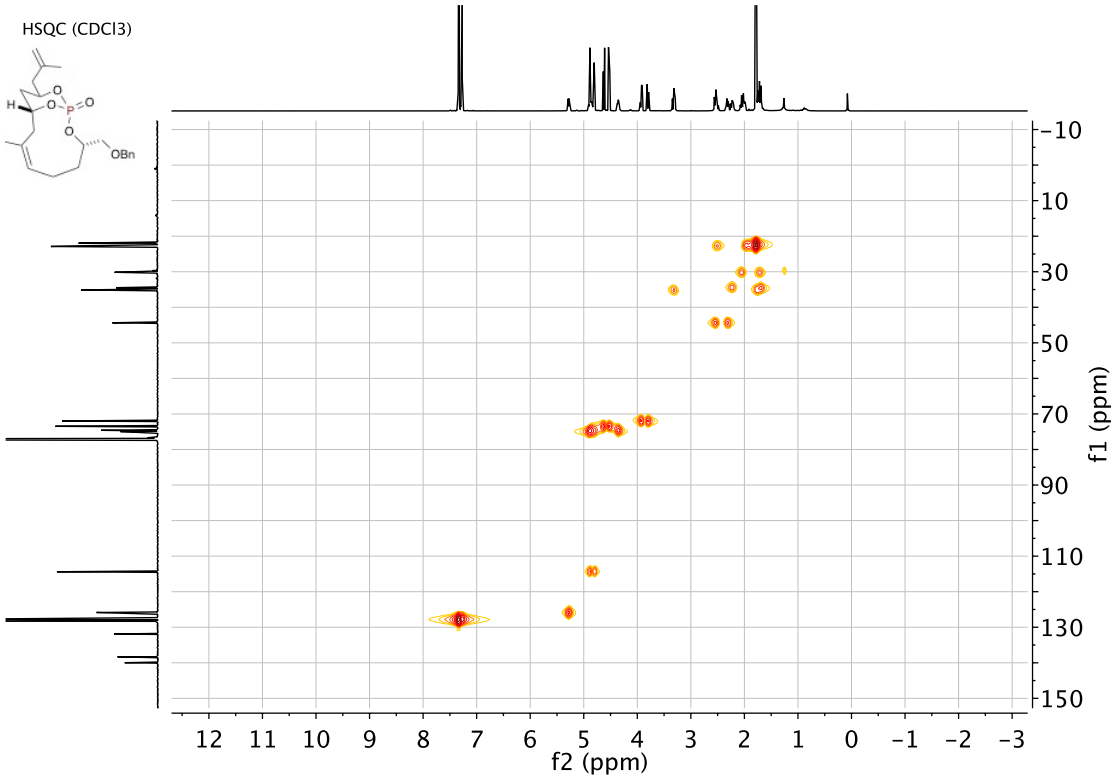


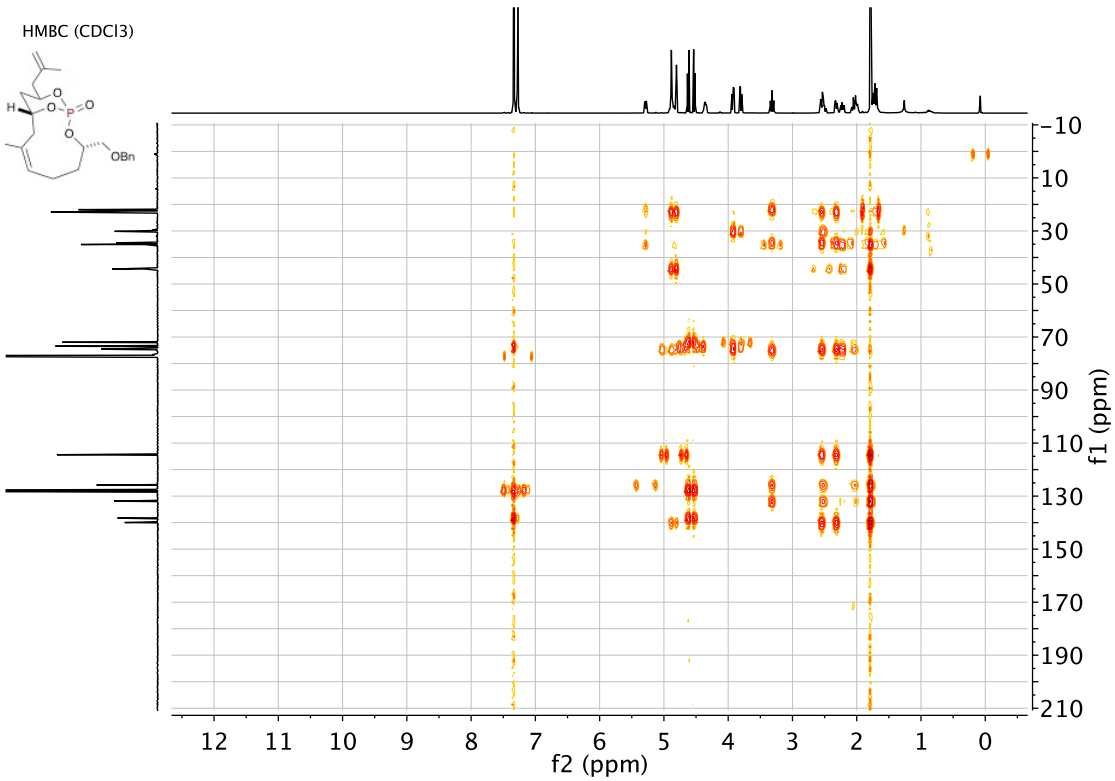

139.97
138.31
131.91
128.27
127.71
127.51
125.85
114.39
77.25
77.00
76.75
75.02
74.96
74.66
74.61
74.61
74.57
73.48
71.99
44.36
44.29
35.12
34.48
34.43
30.23
30.15
22.89
22.69
21.95
13C NMR (126 MHz, CDCl3)
OBn
250000
200000
150000
100000
50000
0
70 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)

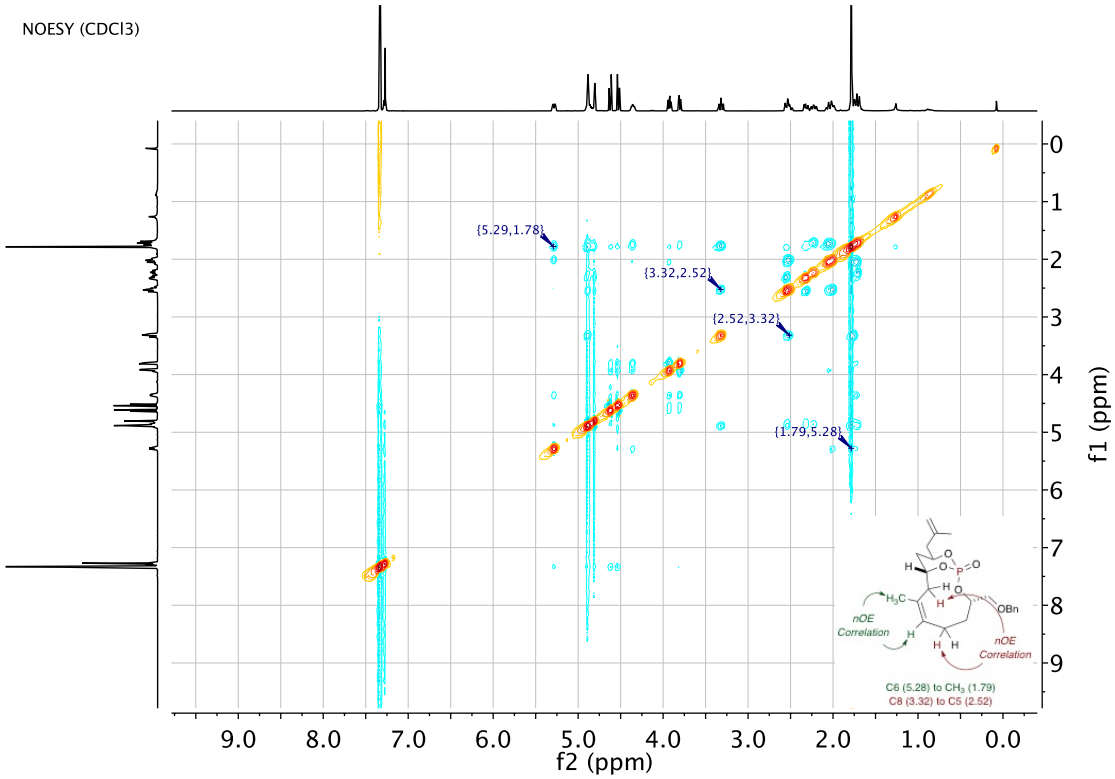

128.33
127.77
127.56
125.90
114.45
75.08
75.01
74.71
74.67
74.65
74.63
73.53
72.04
44.41
44.34
35.17
34.54
34.48
30.28
30.20
22.95
22.74
22.00
13C {1H} NMR (126 MHz, CDCl3)
OBn
70000
60000
50000
40000
30000
20000
10000
0
−10000
−20000
−30000
−40000
−50000
−60000
70 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)


31P NMR (162 MHz, CDCl3)
9.45
9.60
OBn
1800
1600
1400
1200
1000
800
600
400
200
0
-200
90
60
30
0
-30
-60
-90
-120
-150
-180
-210
f1 (ppm)

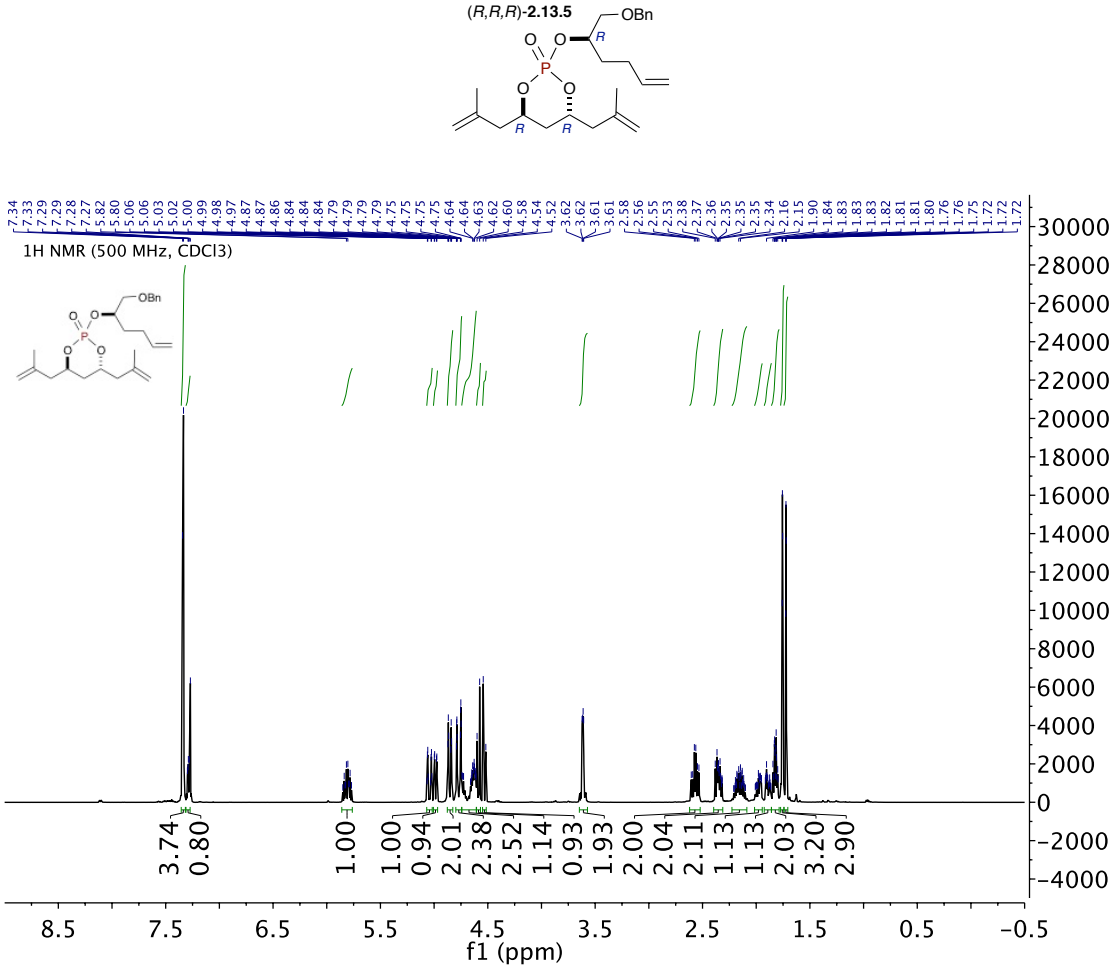

COSY (CDCl3)
OBn
0
1
2
3
4
5
6
7
8
9
10
11
12
f1 (ppm)
12
11
10
9
8
7
6
5
4
3
2
1
0
f2 (ppm)

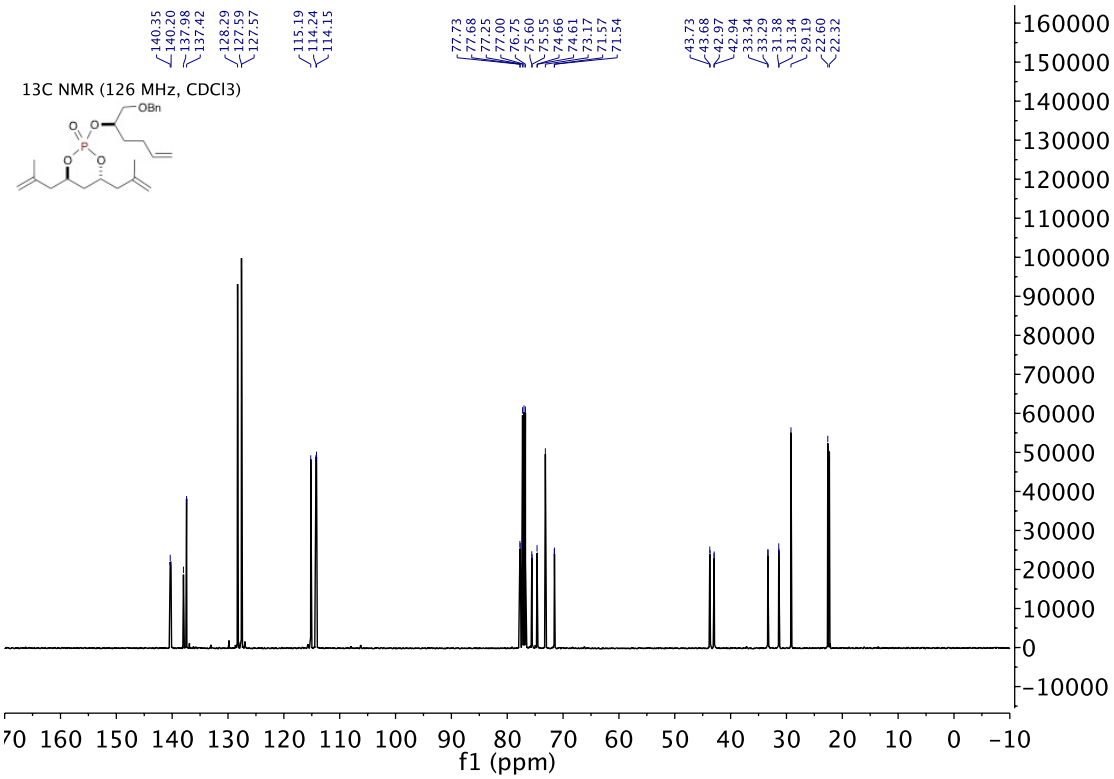

HSQC (CDCl3)
OBn
f2 (ppm)
f1 (ppm)

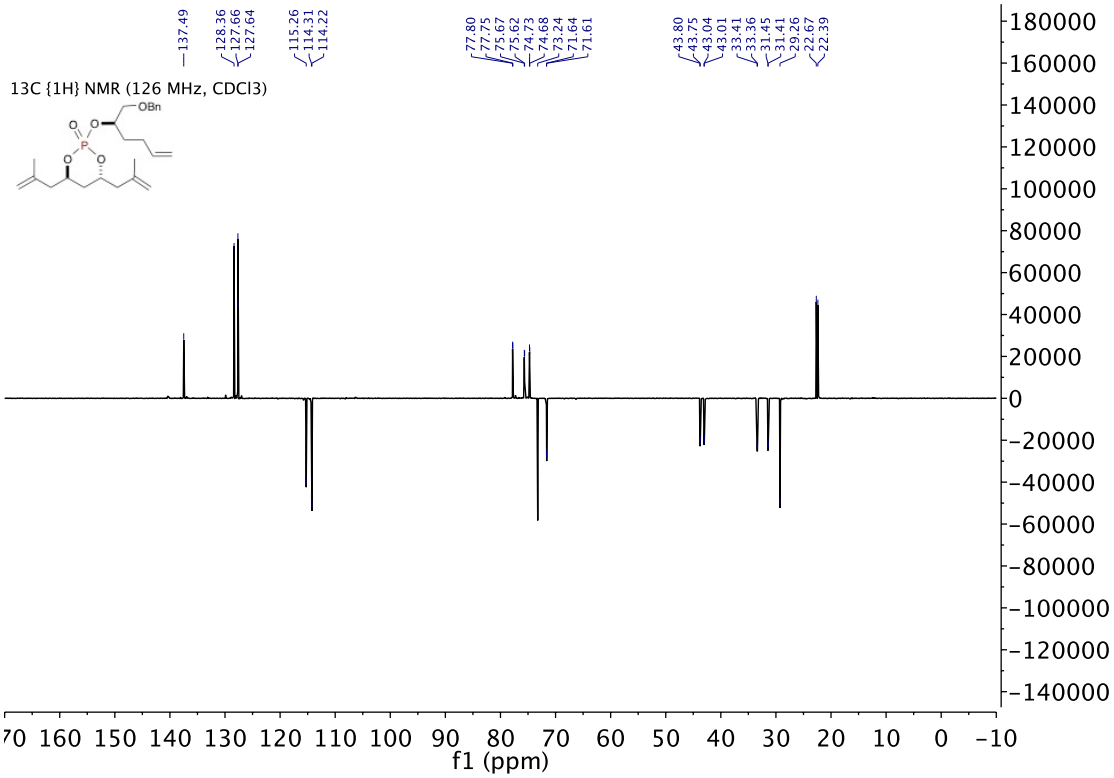

HMBC (CDCl3)
OBn
f2 (ppm)
f1 (ppm)

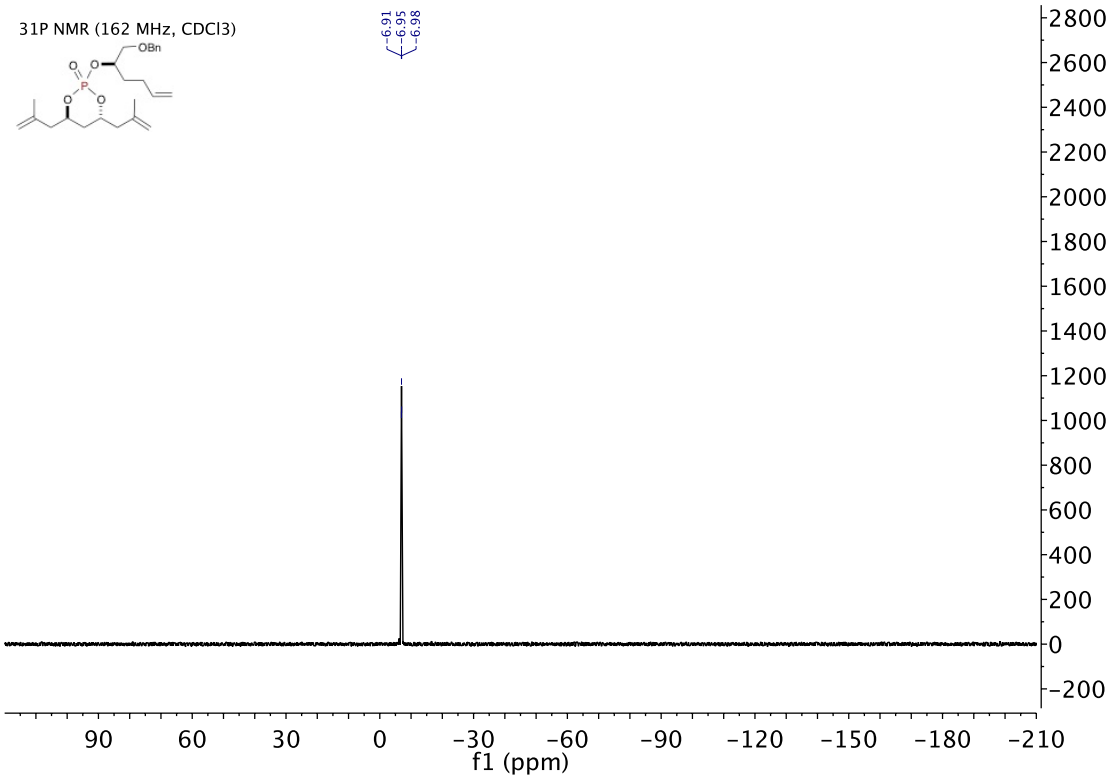

NOESY (CDCl3)
{5.29,1.78}
{3.32,2.52}
{2.52,3.32}
{1.79,5.28}
nOE Correlation
nOE Correlation
OBn
C6 (5.28) to CH3 (1.79)
C8 (3.32) to C5 (2.52)
f2 (ppm)
f1 (ppm)

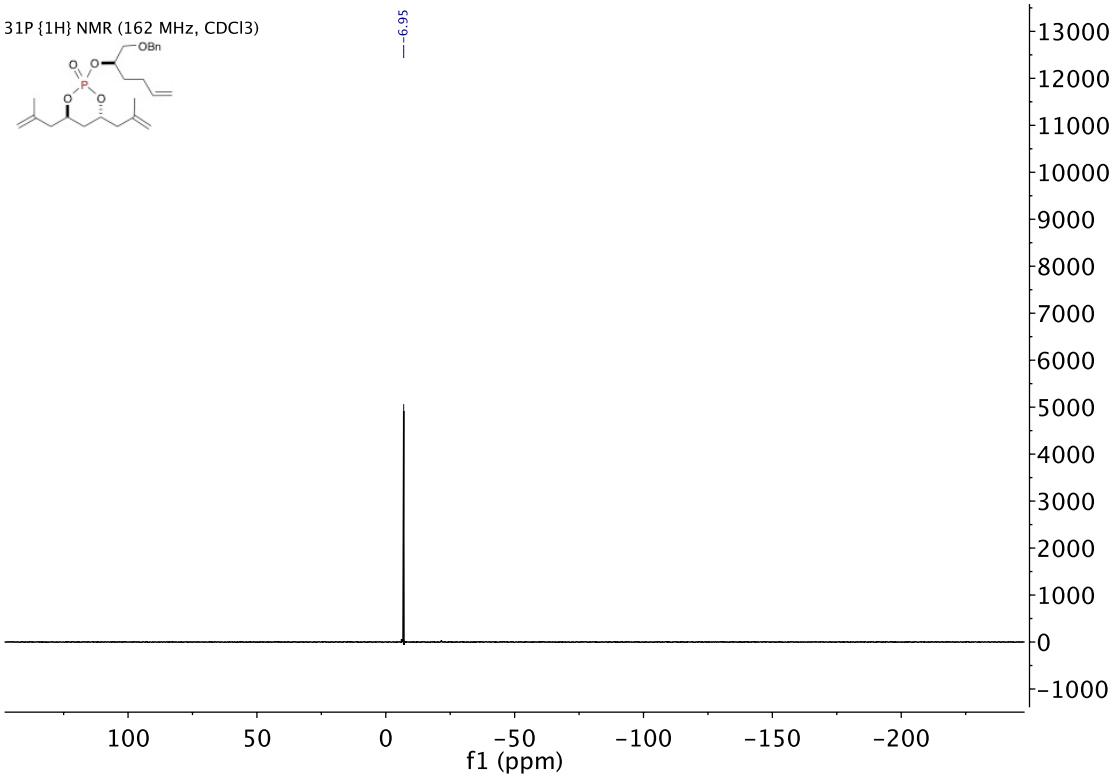
**(4*R*,6*R*)-2-(((*R*)-1-(benzyloxy)hex-5-en-2-yl)oxy)-4,6-bis(2-methylallyl)-1,3,2-dioxaphosphinane 2-oxide (2.13.5)**

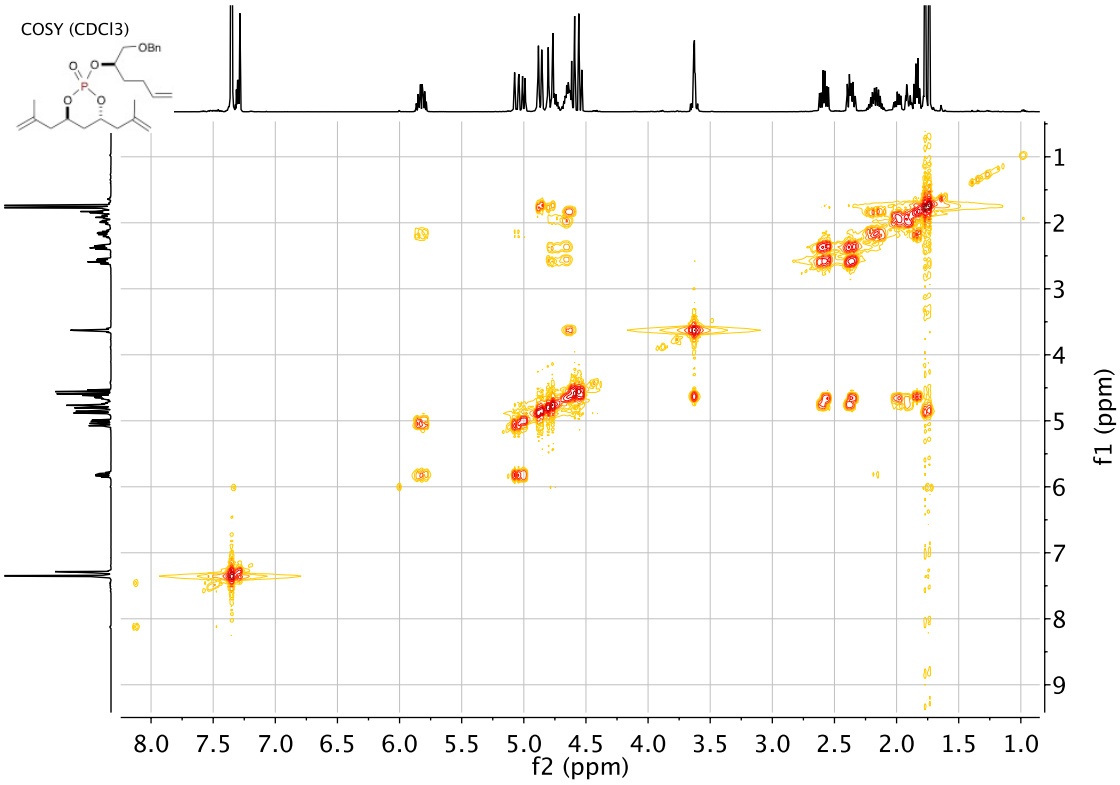


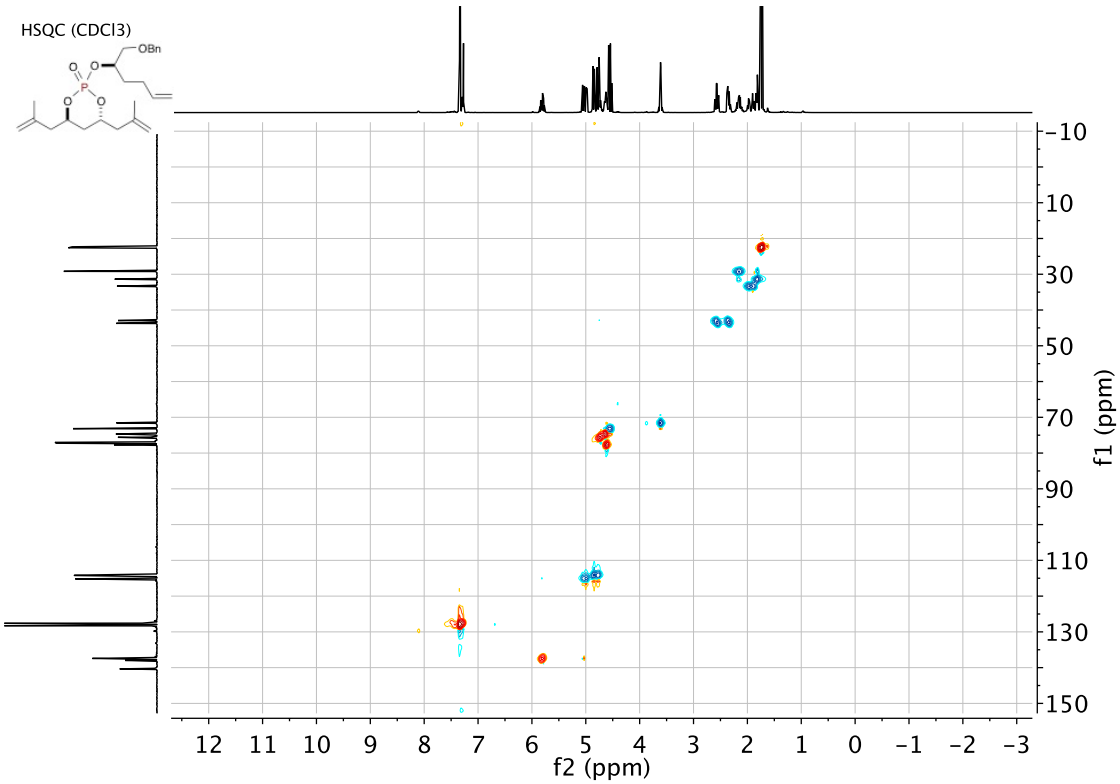

13C NMR (126 MHz, CDCl3)
OBn
140.35
140.20
137.98
137.42
128.29
127.59
127.57
115.19
114.24
114.15
77.73
77.68
77.25
77.00
76.75
75.60
75.55
74.66
74.61
73.17
71.57
71.54
43.73
43.68
42.97
42.94
33.34
33.29
31.38
31.34
29.19
22.60
22.32
f1 (ppm)


13C {1H} NMR (126 MHz, CDCl3)
OBn
137.49
128.36
127.66
127.64
115.26
114.31
114.22
77.80
77.75
75.67
75.62
74.73
74.68
73.24
71.64
71.61
43.80
43.75
43.04
43.01
33.41
33.36
31.45
31.41
29.26
22.67
22.39
f1 (ppm)

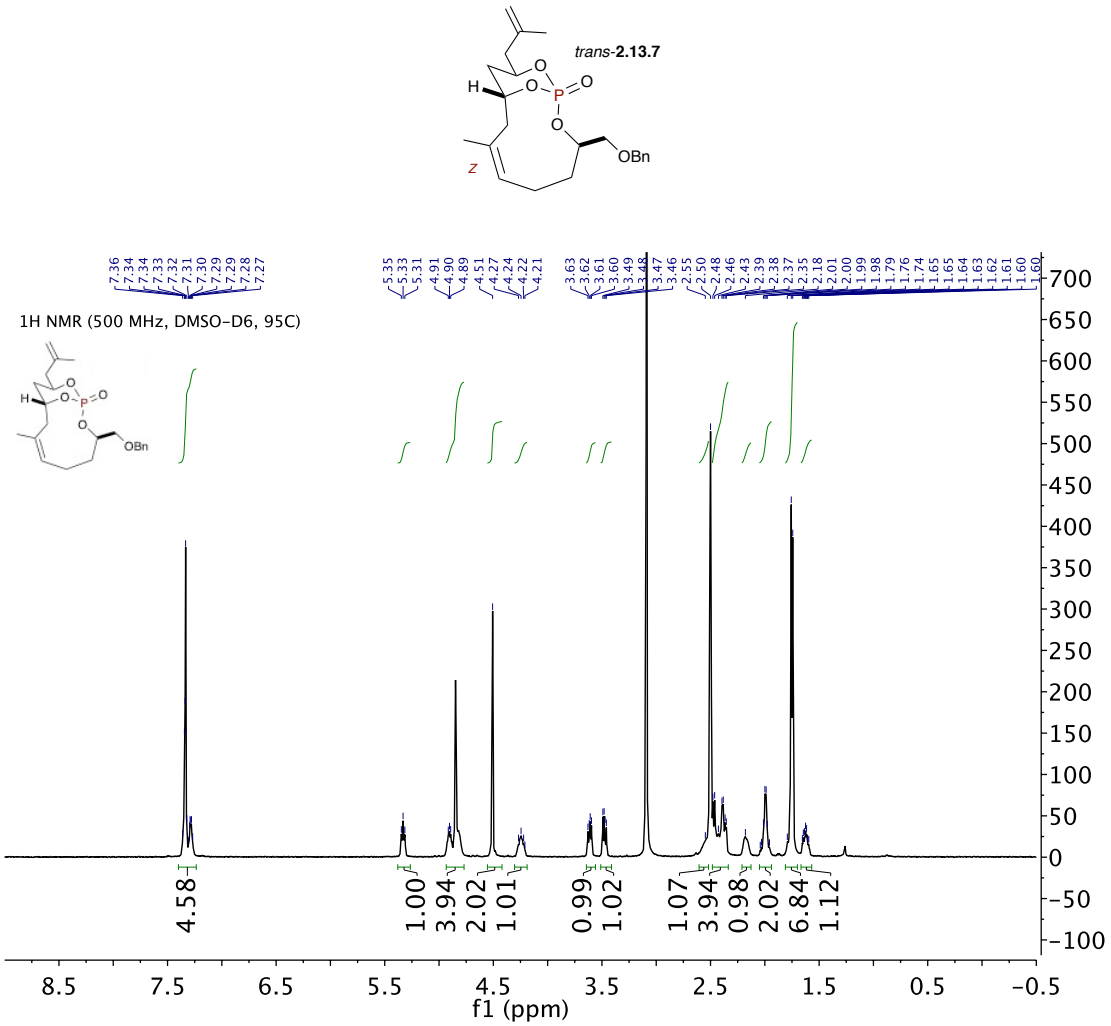

31P NMR (162 MHz, CDCl3)
OBn
-6.91
-6.95
-6.98
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
90
60
30
0
-30
-60
-90
-120
-150
-180
-210
f1 (ppm)

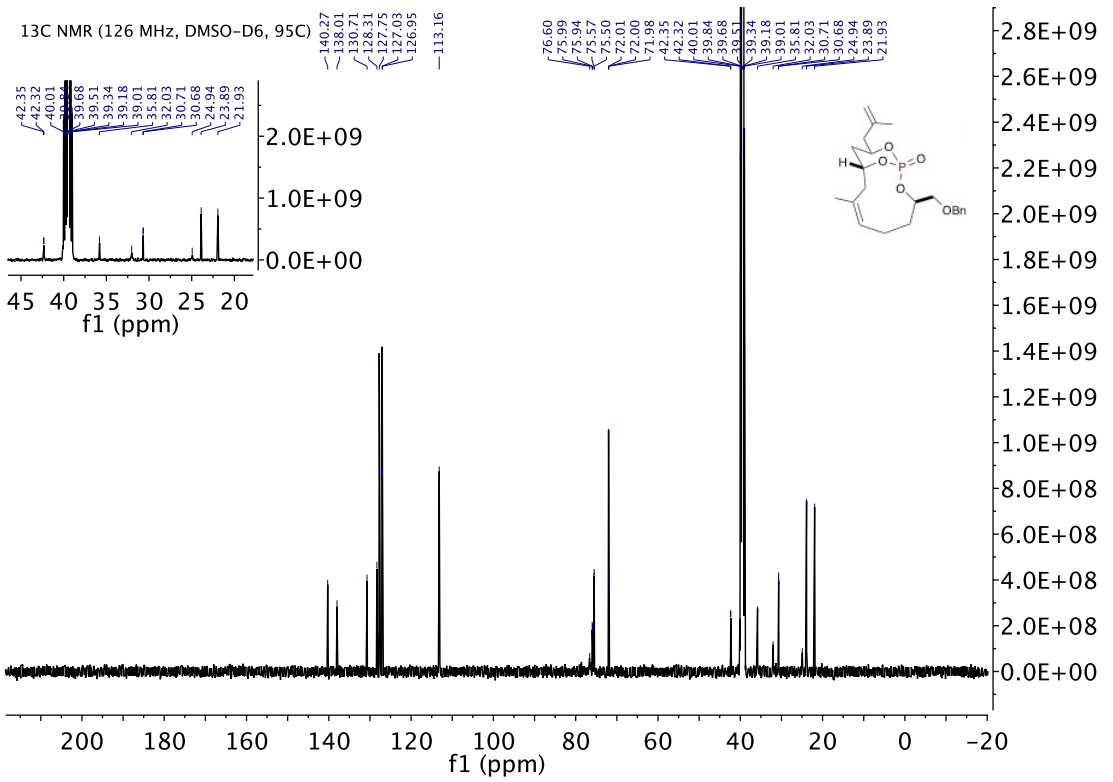

31P {1H} NMR (162 MHz, CDCl3)
OBn
-6.95
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
100
50
0
-50
-100
-150
-200
f1 (ppm)

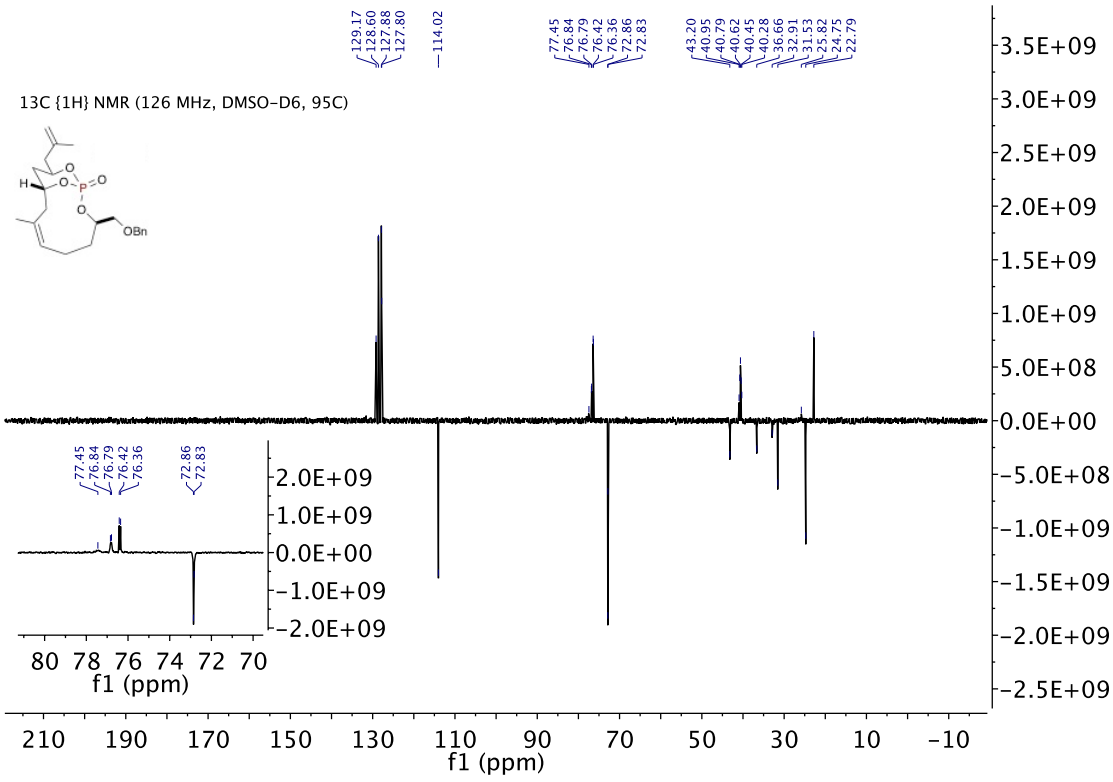

COSY (CDCl3)
OBn
f2 (ppm)
f1 (ppm)

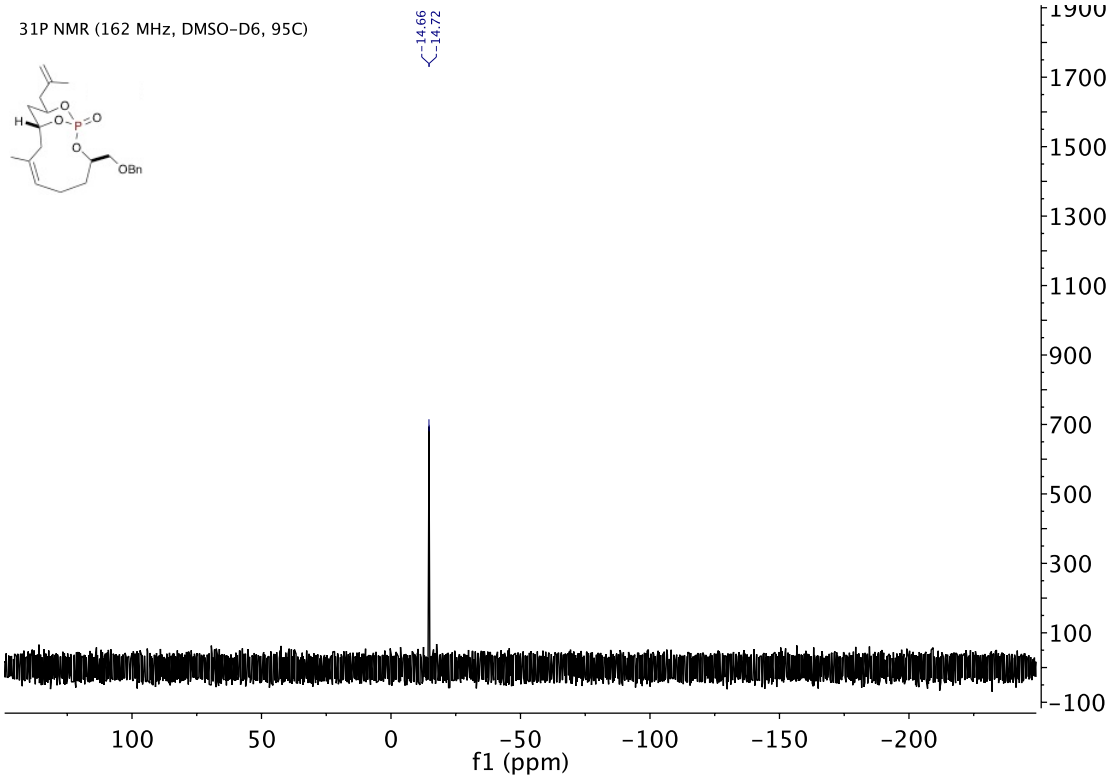

HSQC (CDCl3)
OBn
f2 (ppm)
f1 (ppm)

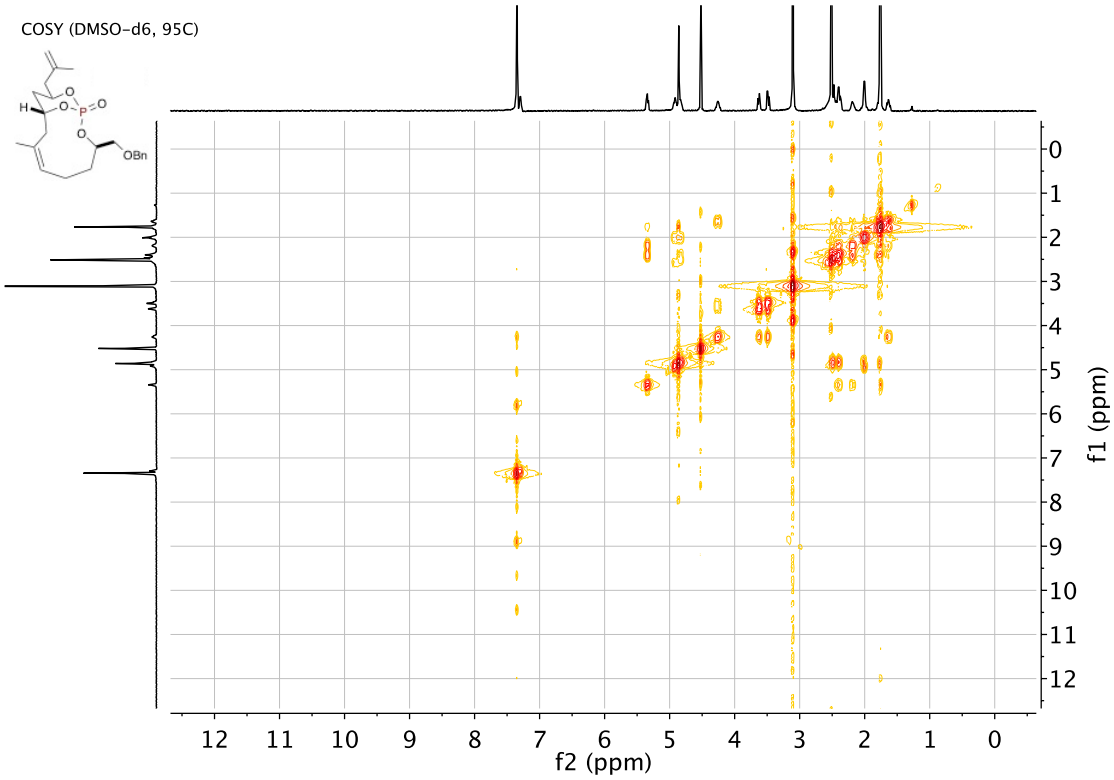
**(1*S*,3*R*,9*R*,11*R*,*Z*)-3-((benzyloxy)methyl)-7-methyl-11-(2-methylallyl)-2,12,13-trioxa-1-phosphabicyclo[7.3.1]tridec-6-ene 1-oxide (*trans*-2.13.7)**

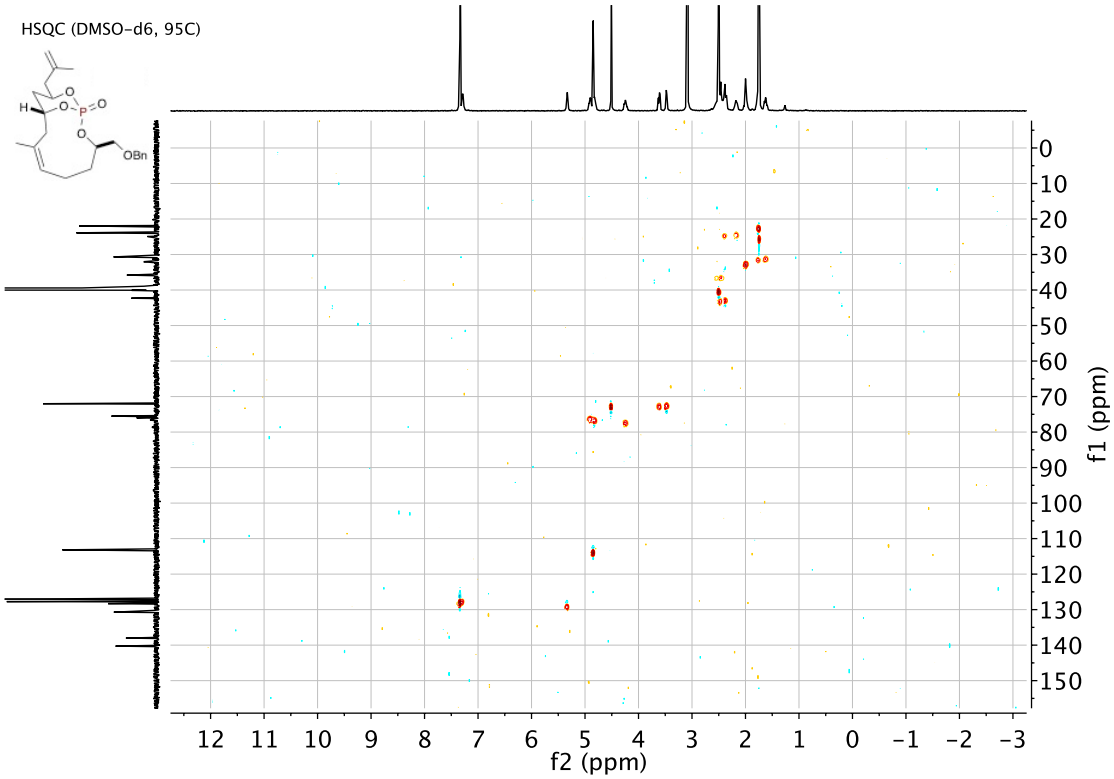


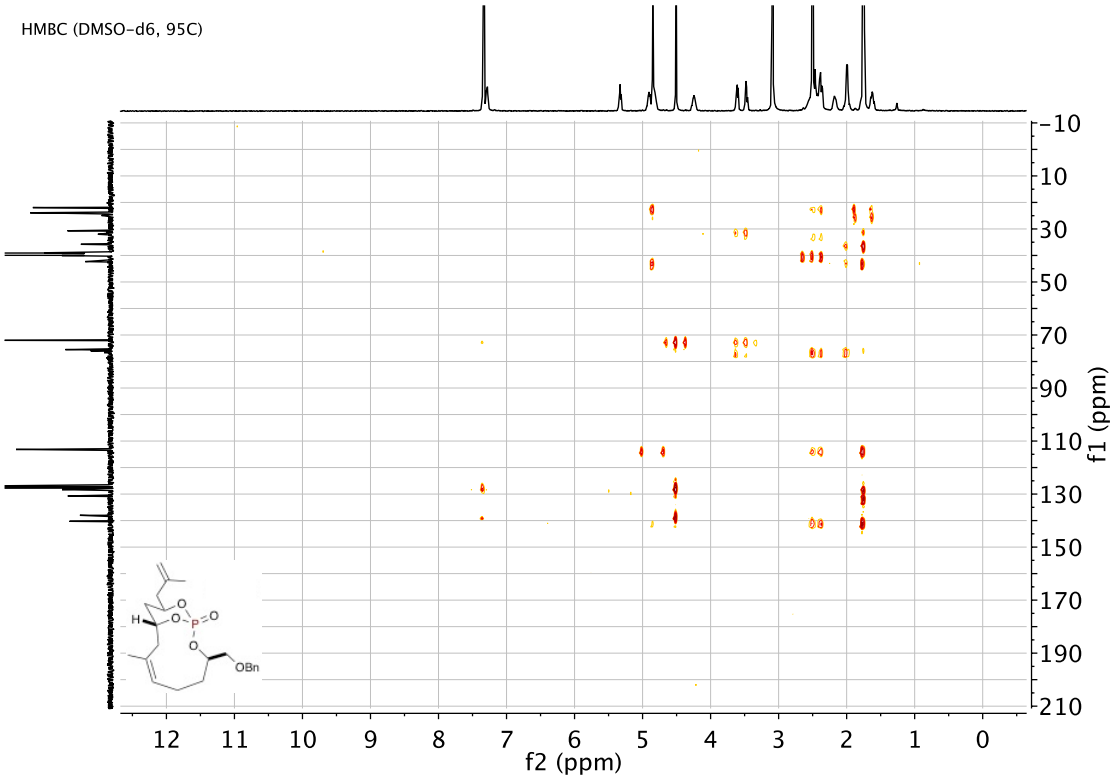

13C NMR (126 MHz, DMSO-D6, 95C)
f1 (ppm)

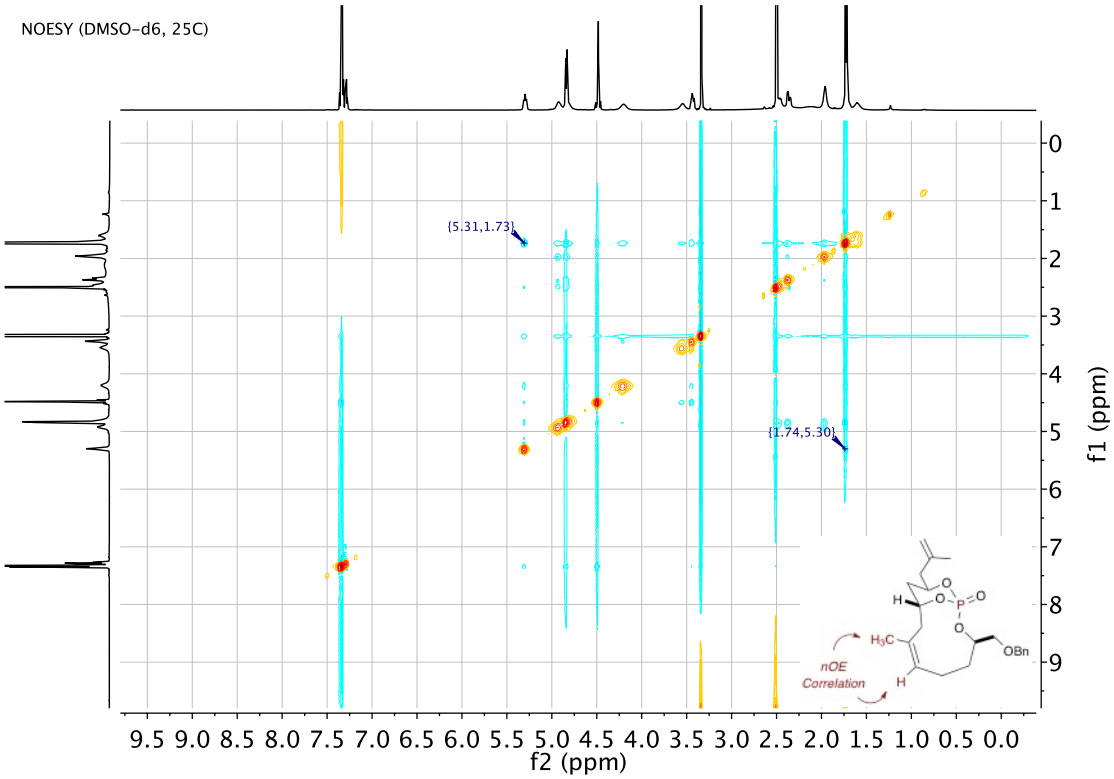

13C {1H} NMR (126 MHz, DMSO-D6, 95C)
f1 (ppm)


31P NMR (162 MHz, DMSO-D6, 95C)
14.66
14.72
OBn
1900
1700
1500
1300
1100
900
700
500
300
100
-100
100
50
0
-50
-100
-150
-200
f1 (ppm)

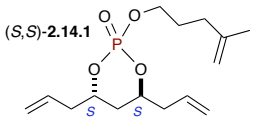

COSY (DMSO-d6, 95C)
OBn
0
1
2
3
4
5
6
7
8
9
10
11
12
f1 (ppm)
12
11
10
9
8
7
6
5
4
3
2
1
0
f2 (ppm)

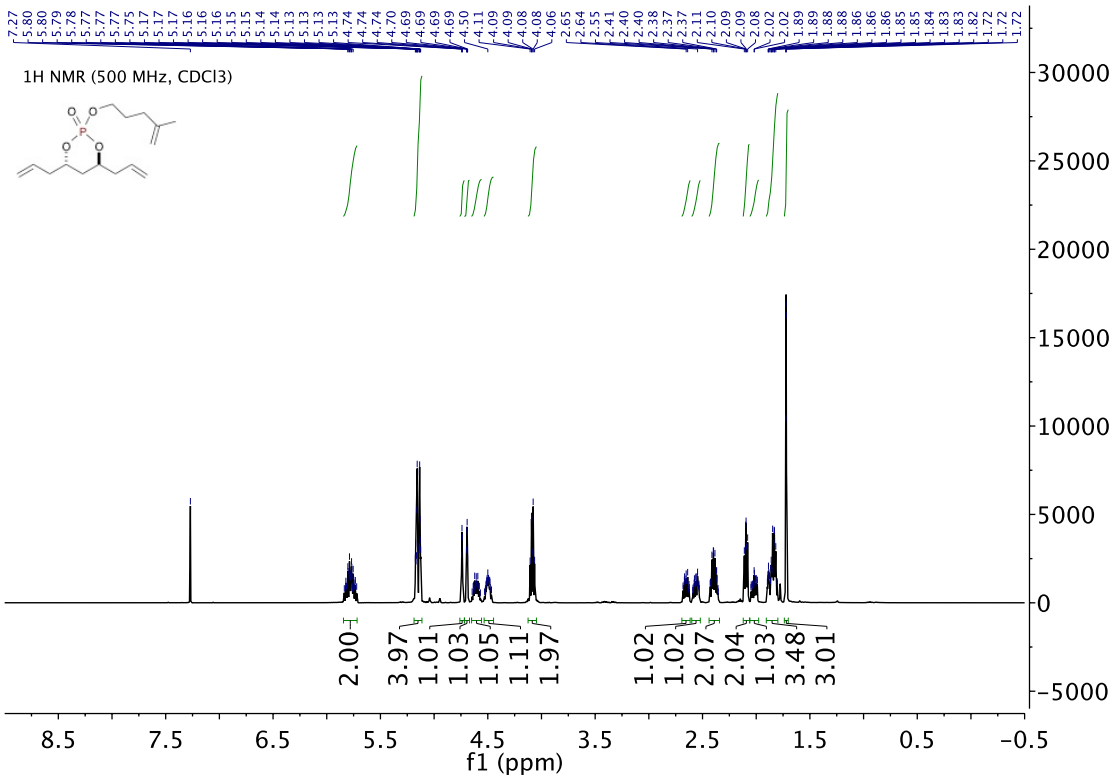

HSQC (DMSO-d6, 95C)
OBn
f2 (ppm)
f1 (ppm)

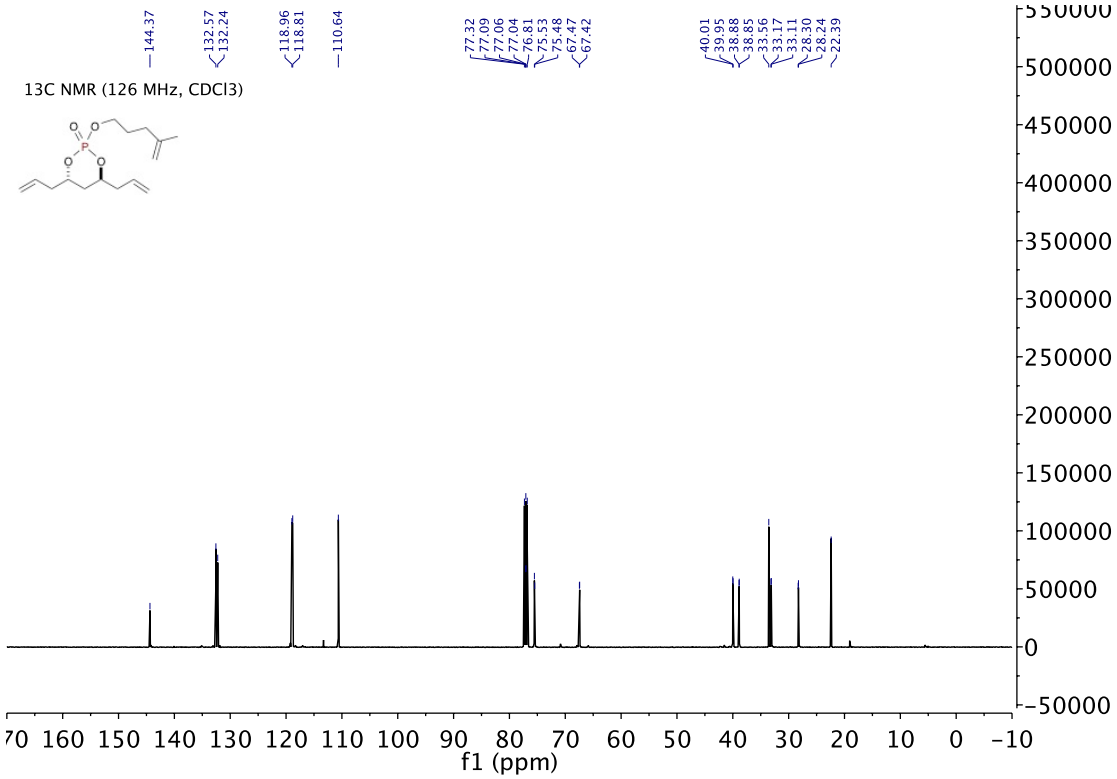

HMBC (DMSO-d6, 95C)
OBn
f2 (ppm)
f1 (ppm)

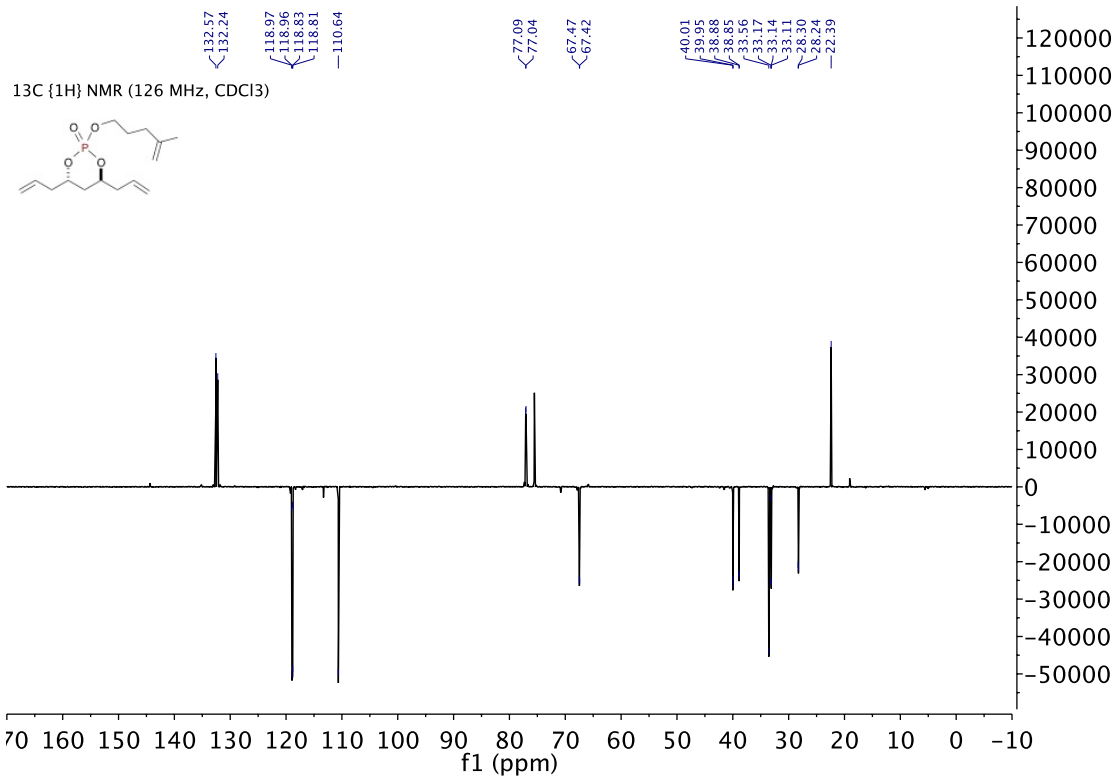

NOESY (DMSO-d6, 25C)
{5.31,1.73}
{1.74,5.30}
f1 (ppm)
f2 (ppm)
nOE
Correlation
H3C
OBn

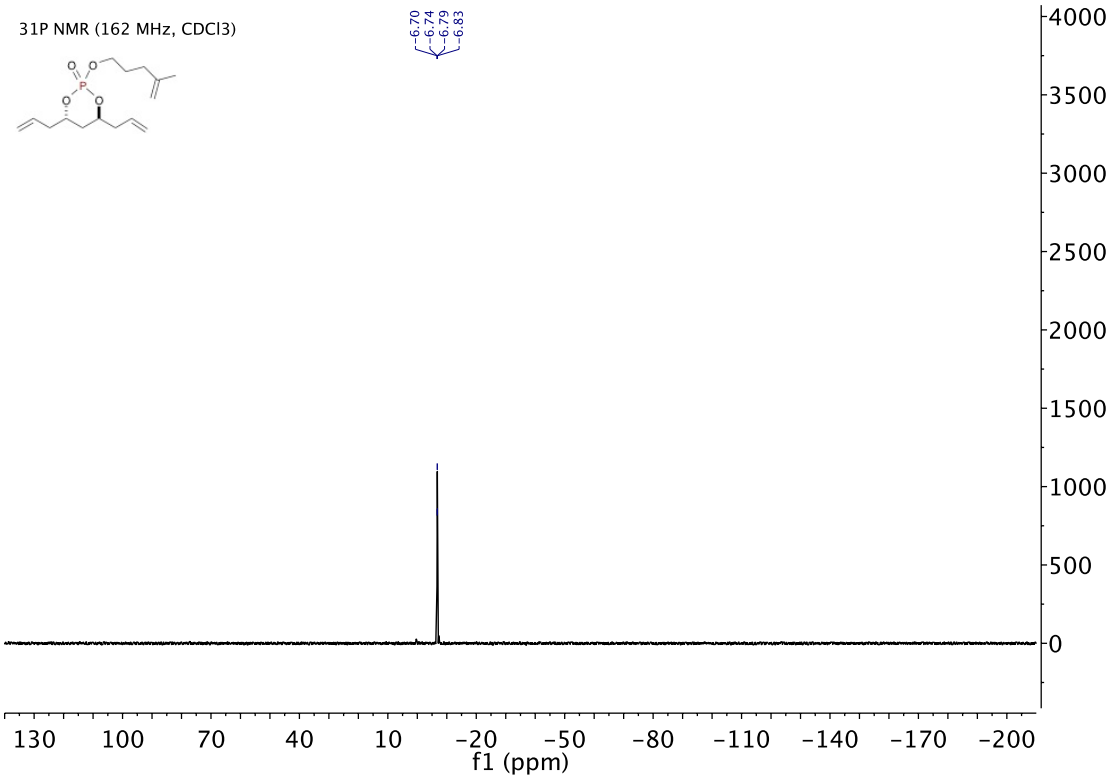
**(4*S*,6*S*)-4,6-diallyl-2-((4-methylpent-4-en-1-yl)oxy)-1,3,2-dioxaphosphinane 2-oxide (2.14.1)**

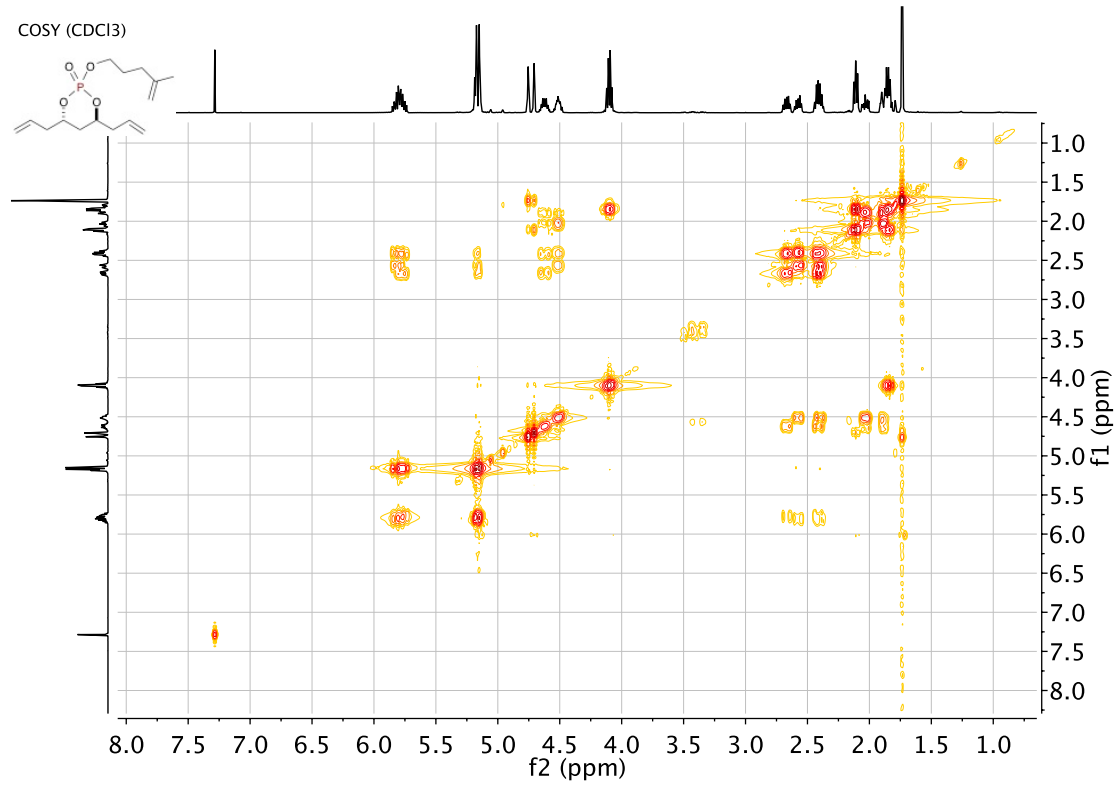


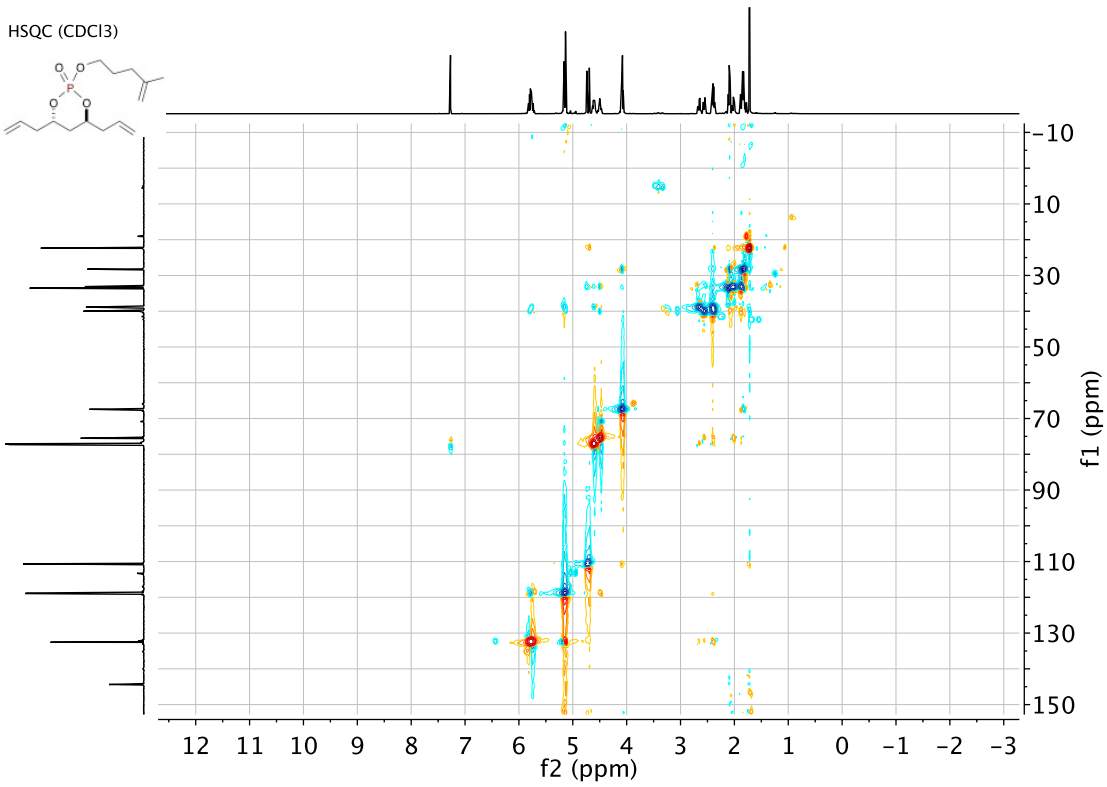




144.37
132.57
132.24
118.96
118.81
110.64
77.32
77.09
77.06
77.04
76.81
75.53
75.48
67.47
67.42
40.01
39.95
38.88
38.85
33.56
33.17
33.11
28.30
28.24
22.39
13C NMR (126 MHz, CDCl3)
f1 (ppm)

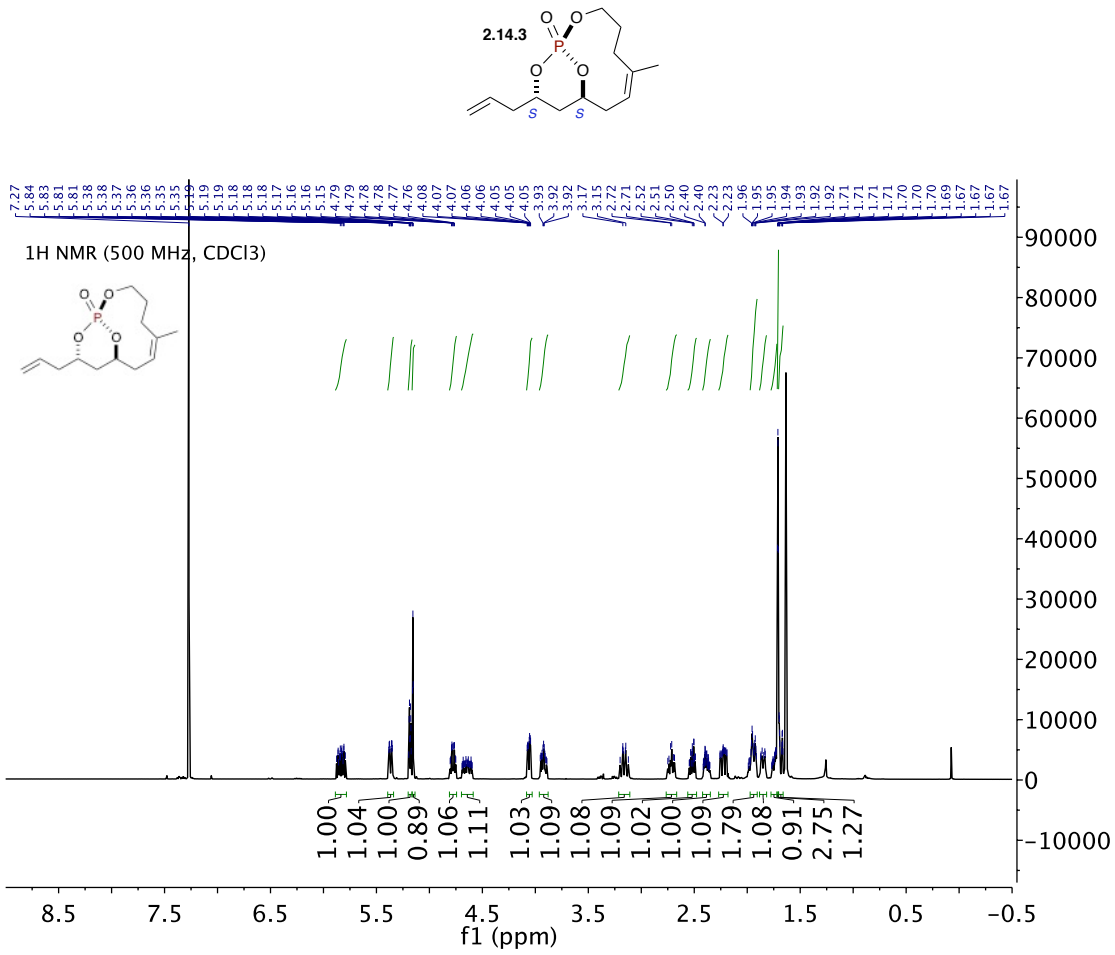

132.57
132.24
118.97
118.96
118.83
118.81
110.64
77.09
77.04
67.47
67.42
40.01
39.95
38.88
38.85
33.56
33.17
33.14
33.11
28.30
28.24
22.39
13C {1H} NMR (126 MHz, CDCl3)
f1 (ppm)

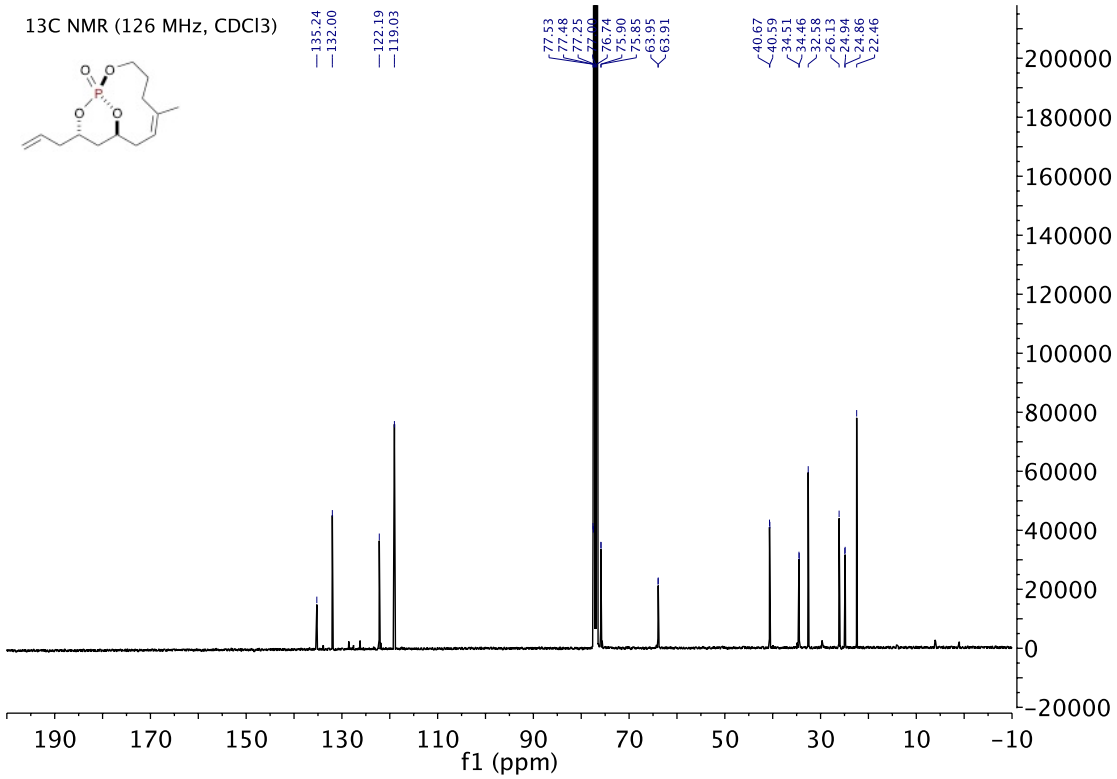

31P NMR (162 MHz, CDCl3)
6.70
6.74
6.79
6.83
4000
3500
3000
2500
2000
1500
1000
500
0
130
100
70
40
10
-20
-50
-80
-110
-140
-170
-200
f1 (ppm)

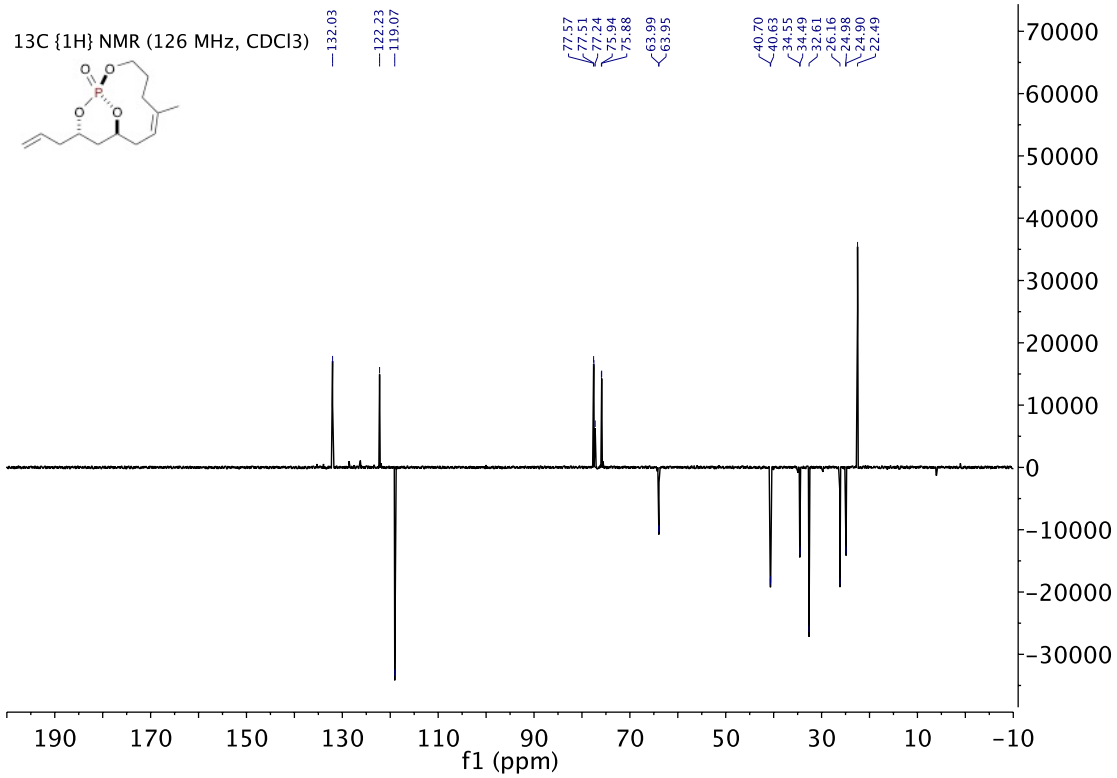

COSY (CDCl3)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)

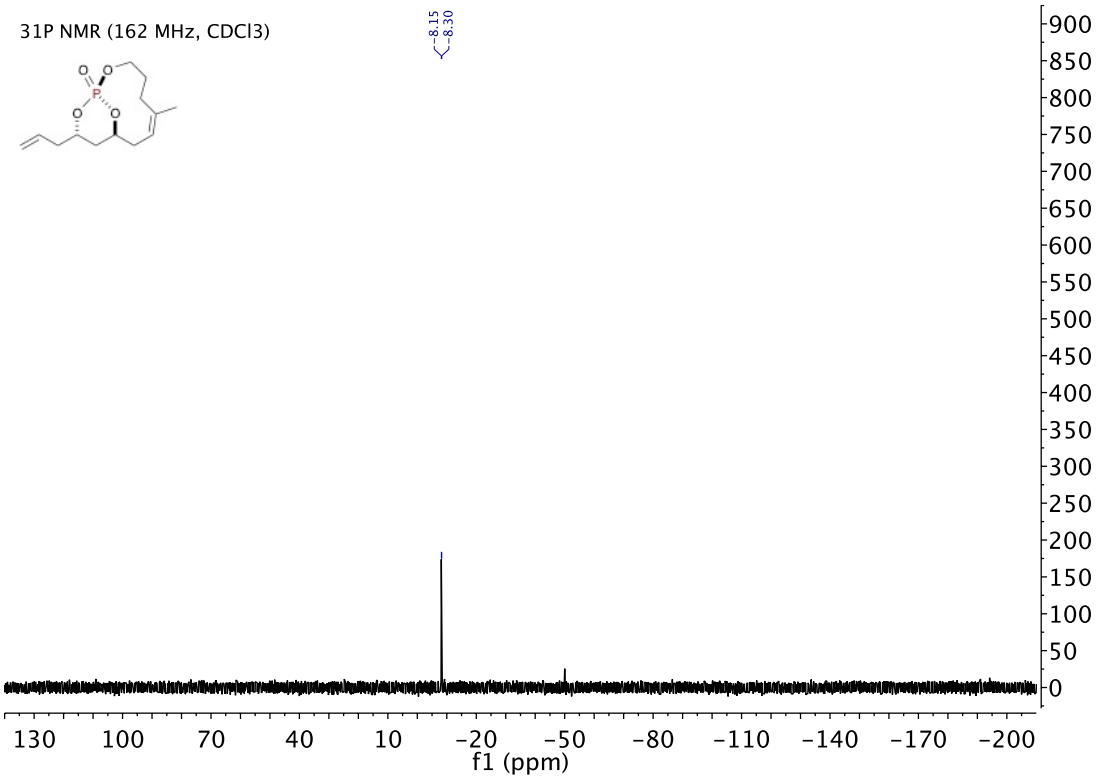

HSQC (CDCl3)
f2 (ppm)
f1 (ppm)
12
11
10
9
8
7
6
5
4
3
2
1
0
−1
−2
−3
−10
10
30
50
70
90
110
130
150

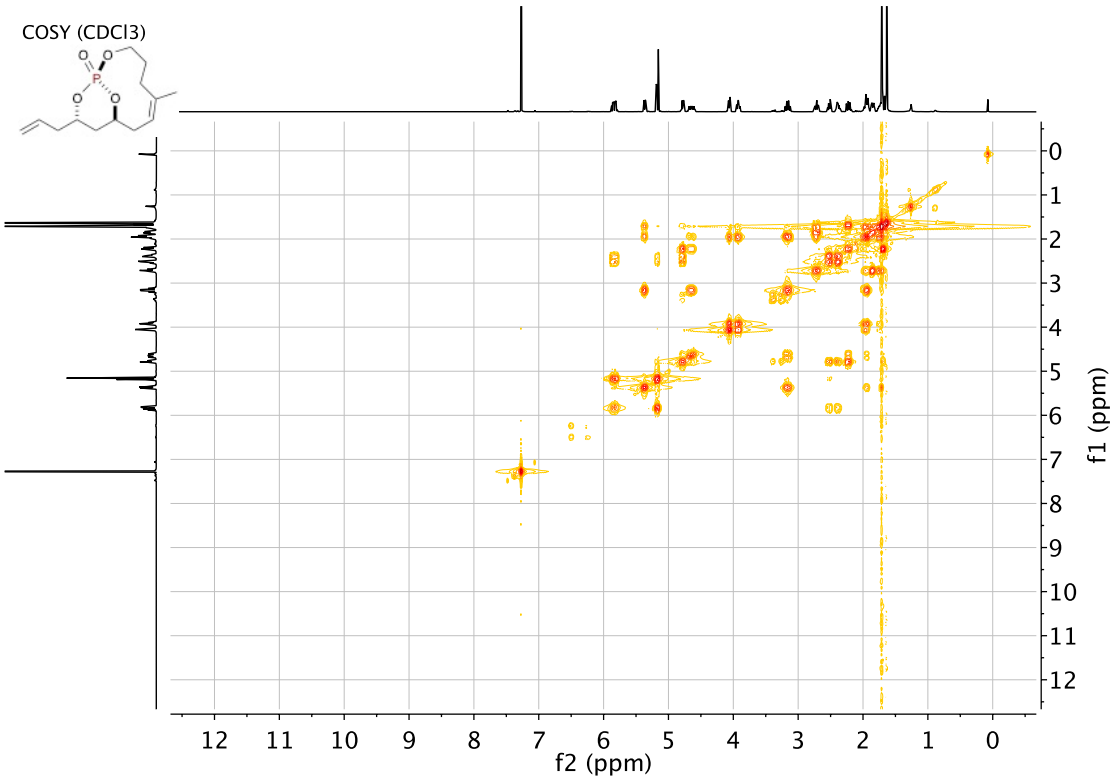
**(1*R*,9*S*,11*S*,*Z*)-11-allyl-6-methyl-2,12,13-trioxa-1-phosphabicyclo[7.3.1]tridec-6-ene 1-oxide (2.14.3)**

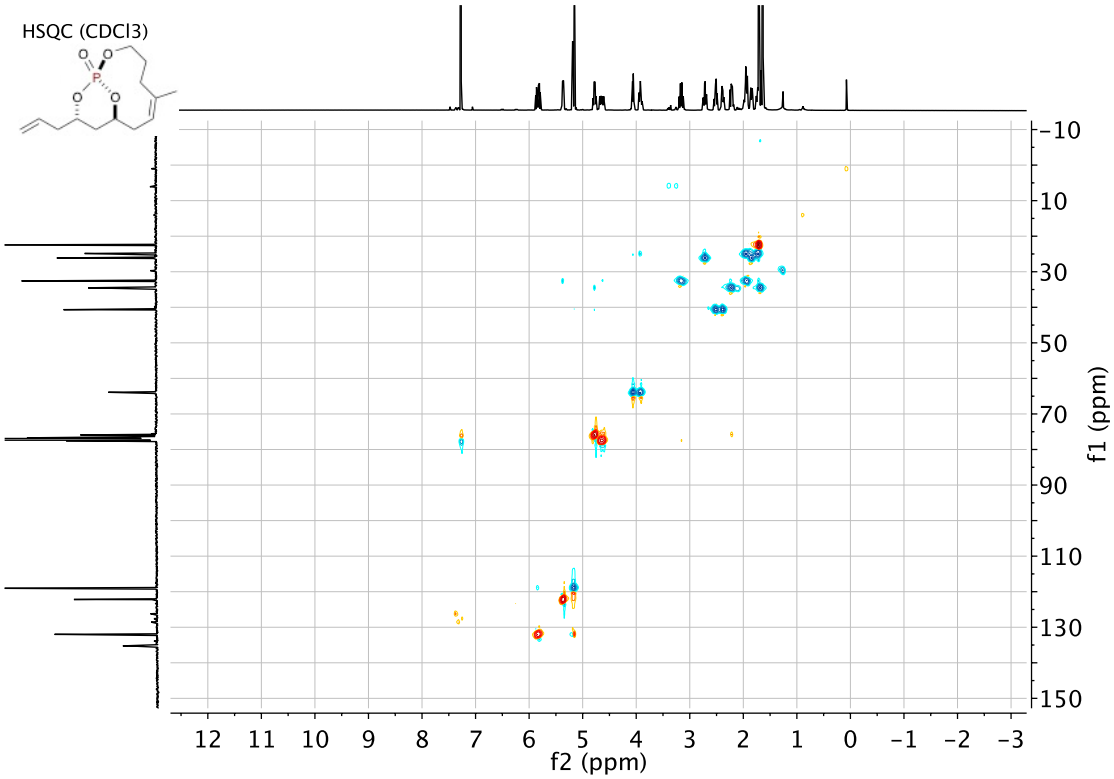


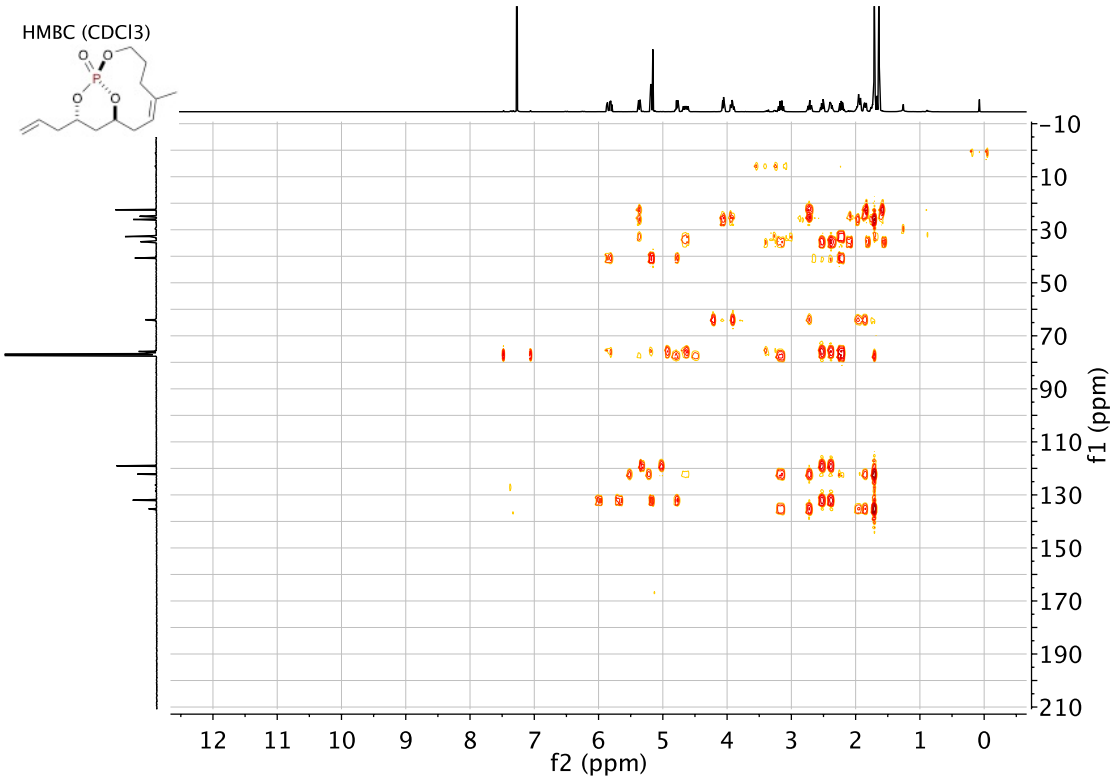

13C NMR (126 MHz, CDCl3)
135.24
132.00
122.19
119.03
77.53
77.48
77.25
77.00
76.74
75.90
75.85
63.95
63.91
40.67
40.59
34.51
34.46
32.58
26.13
24.94
24.86
22.46
200000
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
-20000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

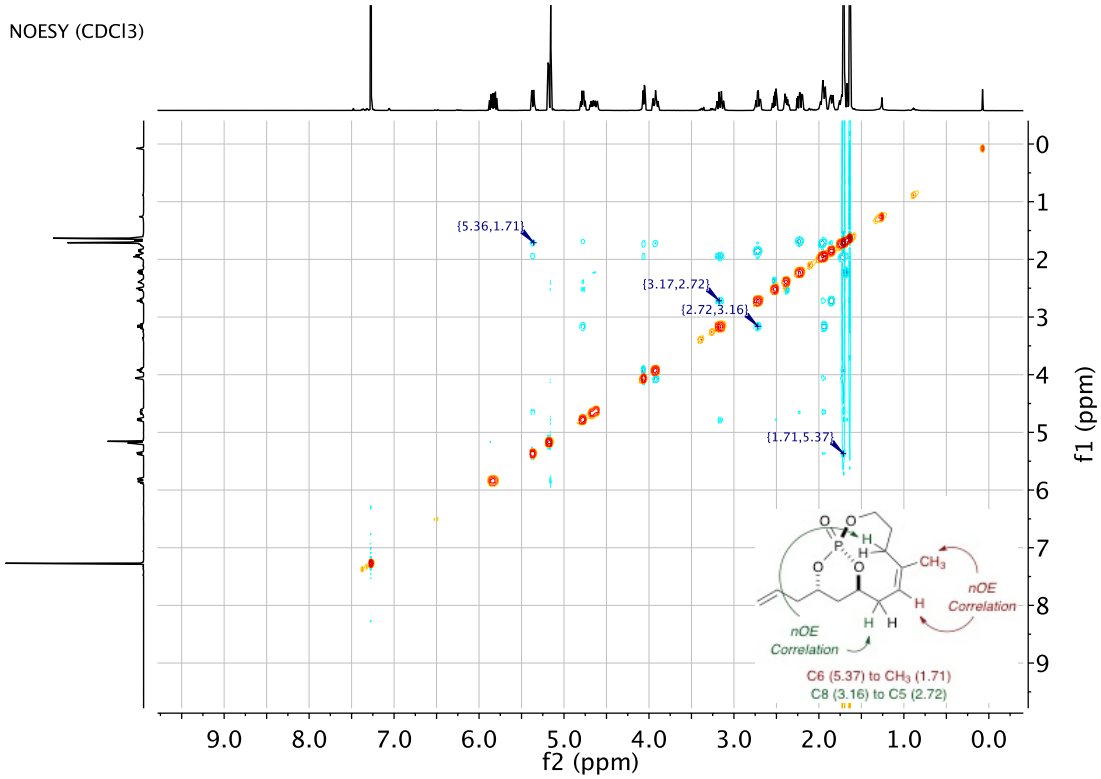

13C {1H} NMR (126 MHz, CDCl3)
132.03
122.23
119.07
77.57
77.51
77.24
75.94
75.88
63.99
63.95
40.70
40.63
34.55
34.49
32.61
26.16
24.98
24.90
22.49
70000
60000
50000
40000
30000
20000
10000
0
-10000
-20000
-30000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)


31P NMR (162 MHz, CDCl3)
8.15
8.30
f1 (ppm)

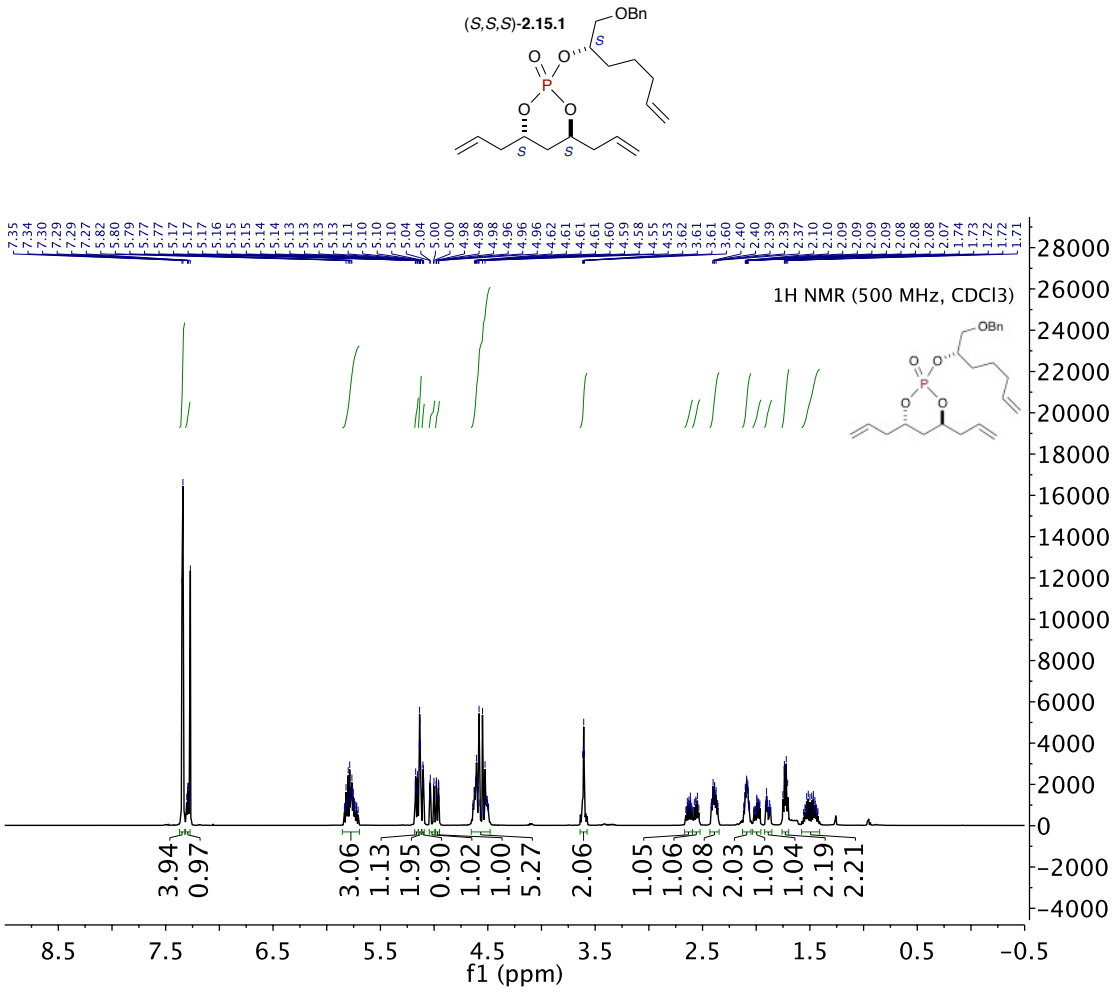

COSY (CDCl3)
f2 (ppm)
f1 (ppm)

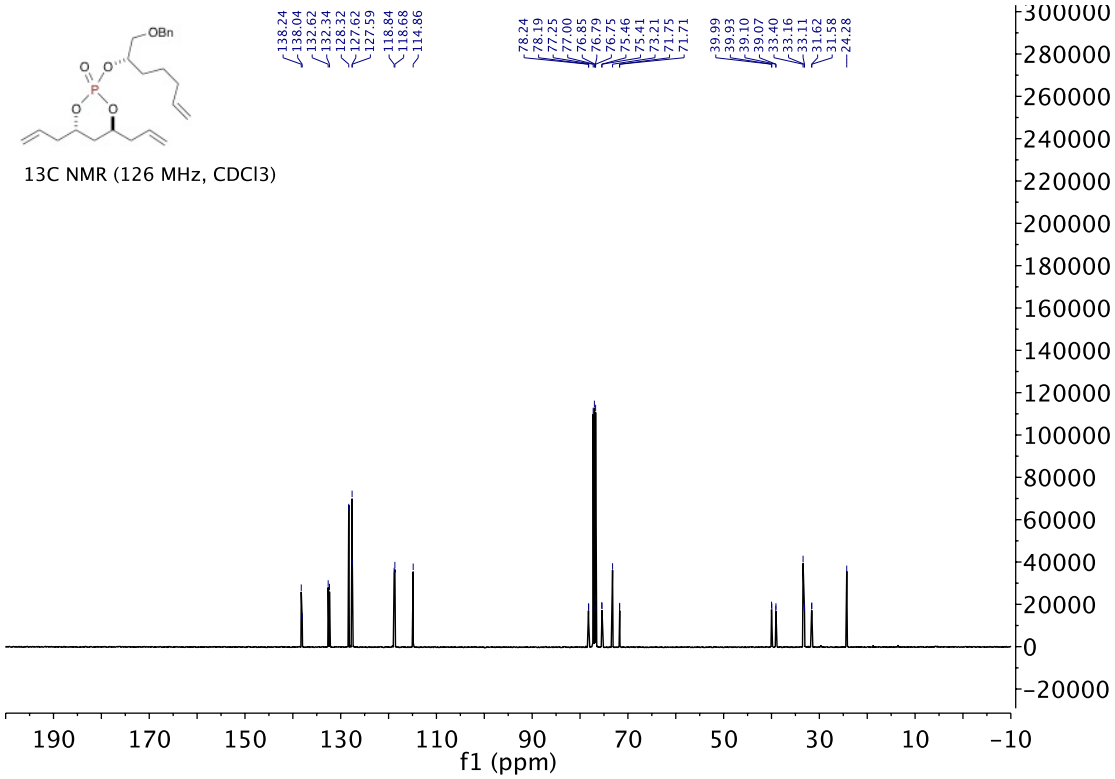

HSQC (CDCl3)
f2 (ppm)
f1 (ppm)


HMBC (CDCl3)
f2 (ppm)
f1 (ppm)

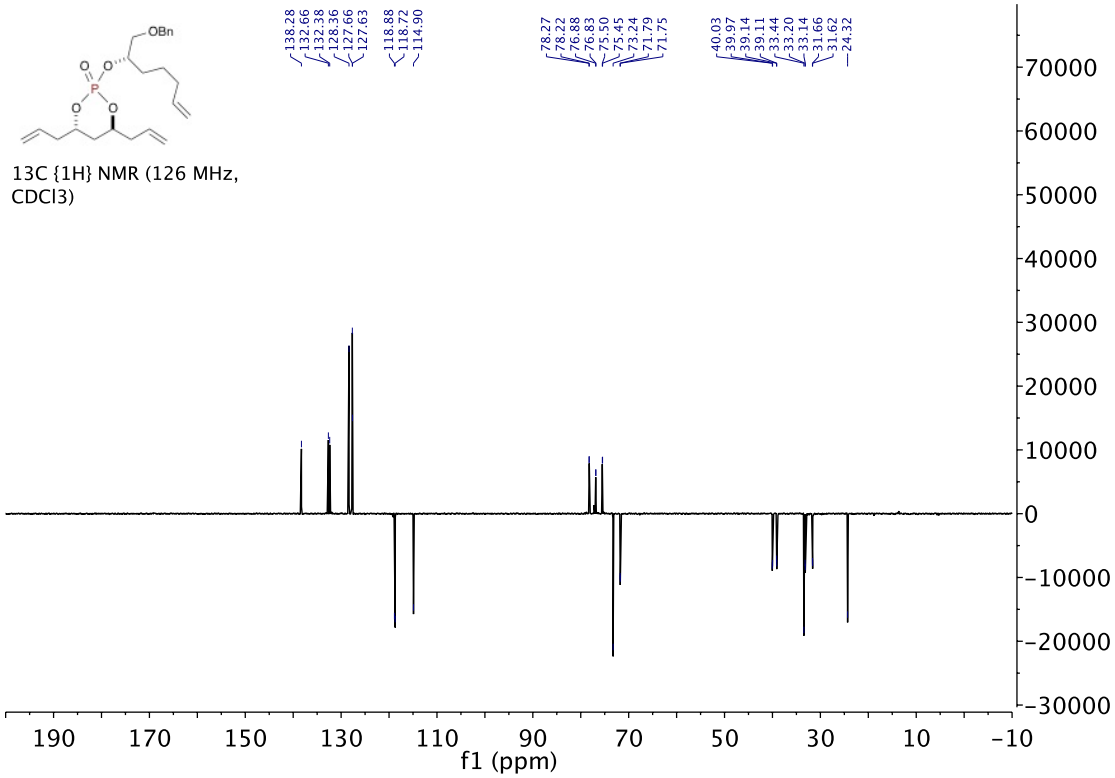

NOESY (CDCl3)
{5.36,1.71}
{3.17,2.72}
{2.72,3.16}
{1.71,5.37}
f2 (ppm)
f1 (ppm)
nOE Correlation
nOE Correlation
C6 (5.37) to CH3 (1.71)
C8 (3.16) to C5 (2.72)

**(4*S*,6*S*)-4,6-diallyl-2-(((*S*)-1-(benzyloxy)hept-6-en-2-yl)oxy)-1,3,2-dioxaphosphinane 2-oxide (2.15.1)**

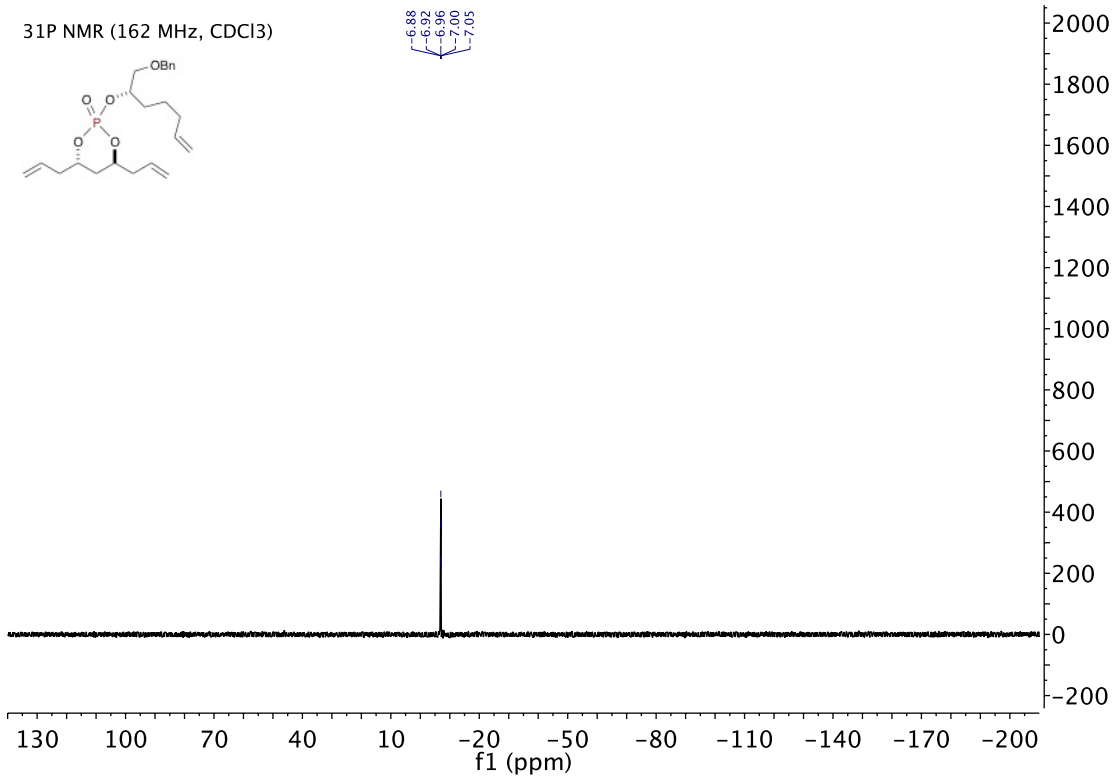


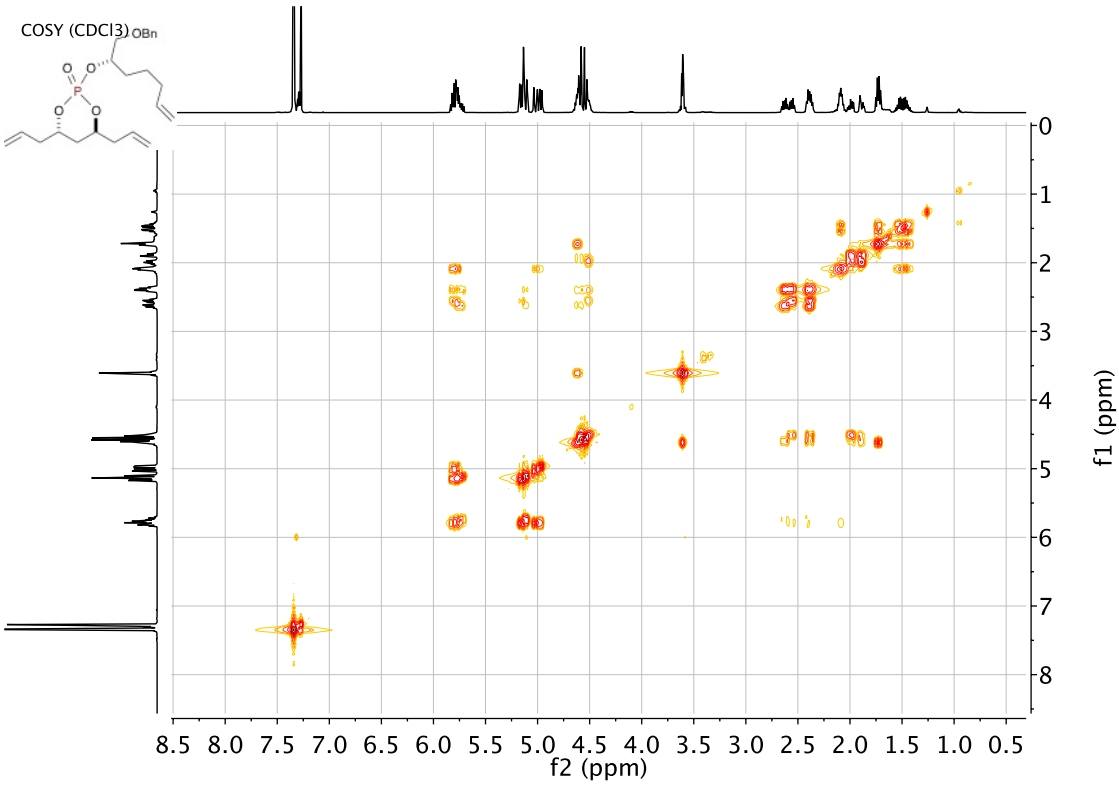


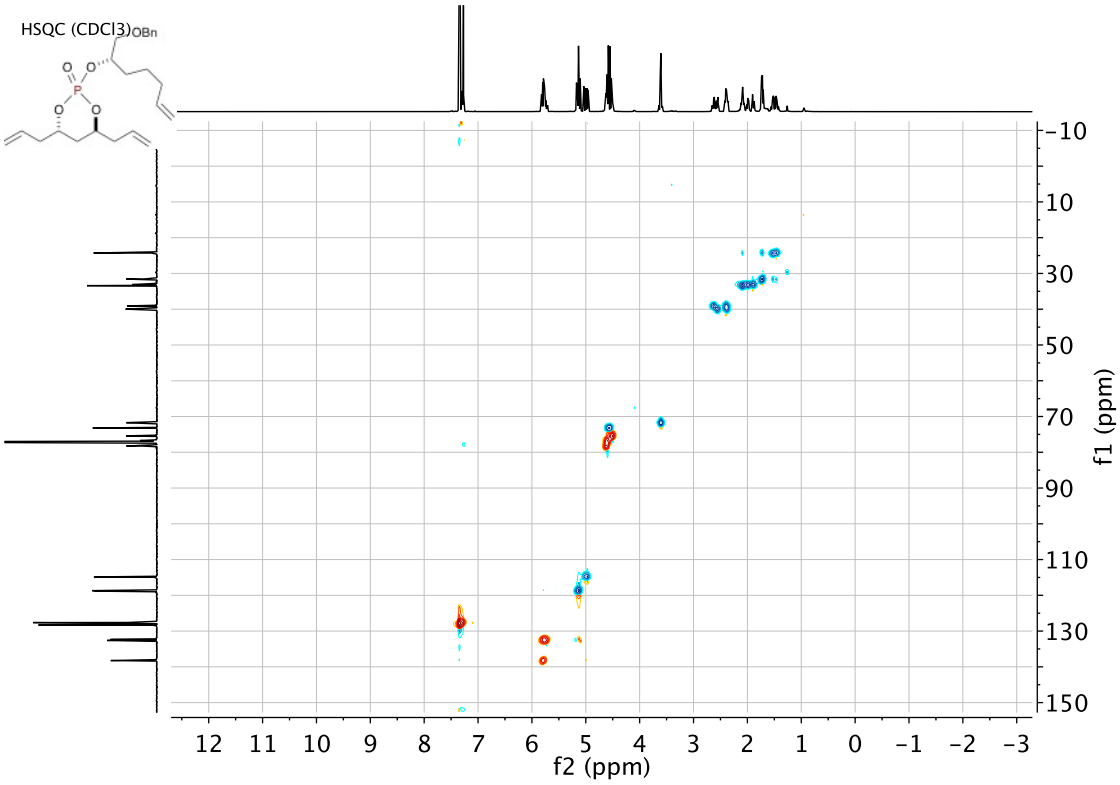

13C NMR (126 MHz, CDCl3)



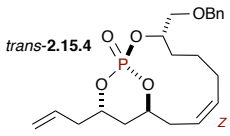

13C {1H} NMR (126 MHz, CDCl3)

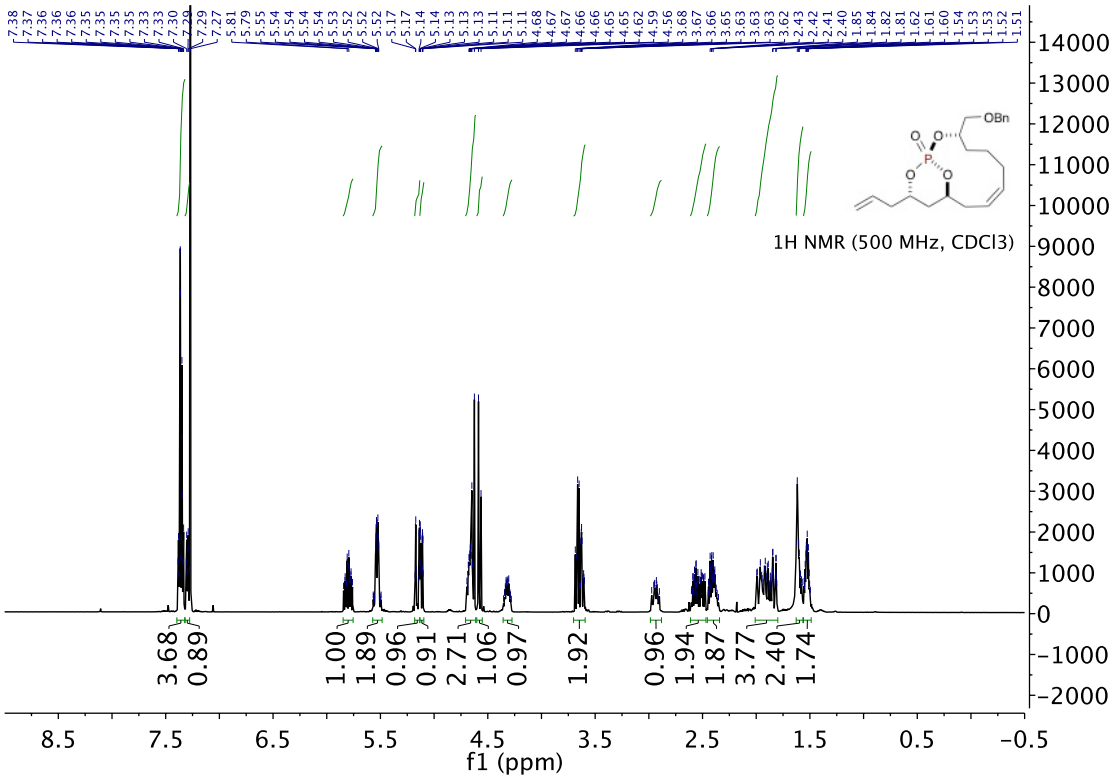

31P NMR (162 MHz, CDCl3)
OBn
6.88
6.92
6.96
7.00
7.05
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
130
100
70
40
10
-20
-50
-80
-110
-140
-170
-200
f1 (ppm)

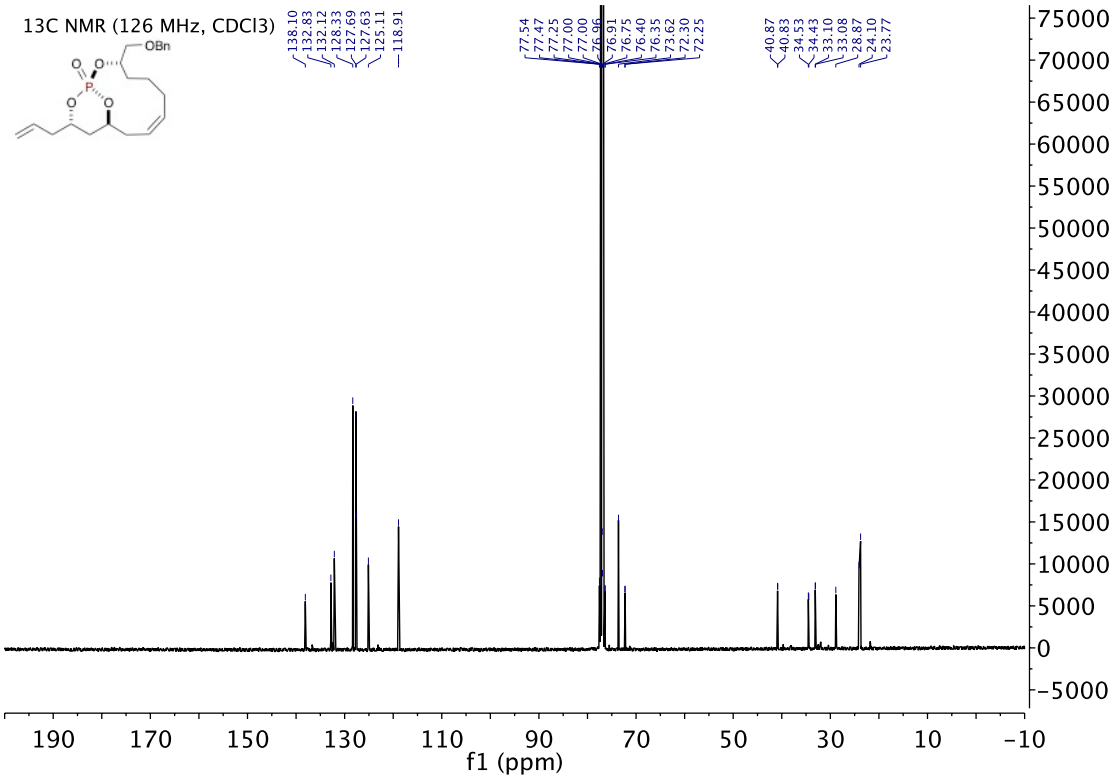

COSY (CDCl3)
OBn
0
1
2
3
4
5
6
7
8
f1 (ppm)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)

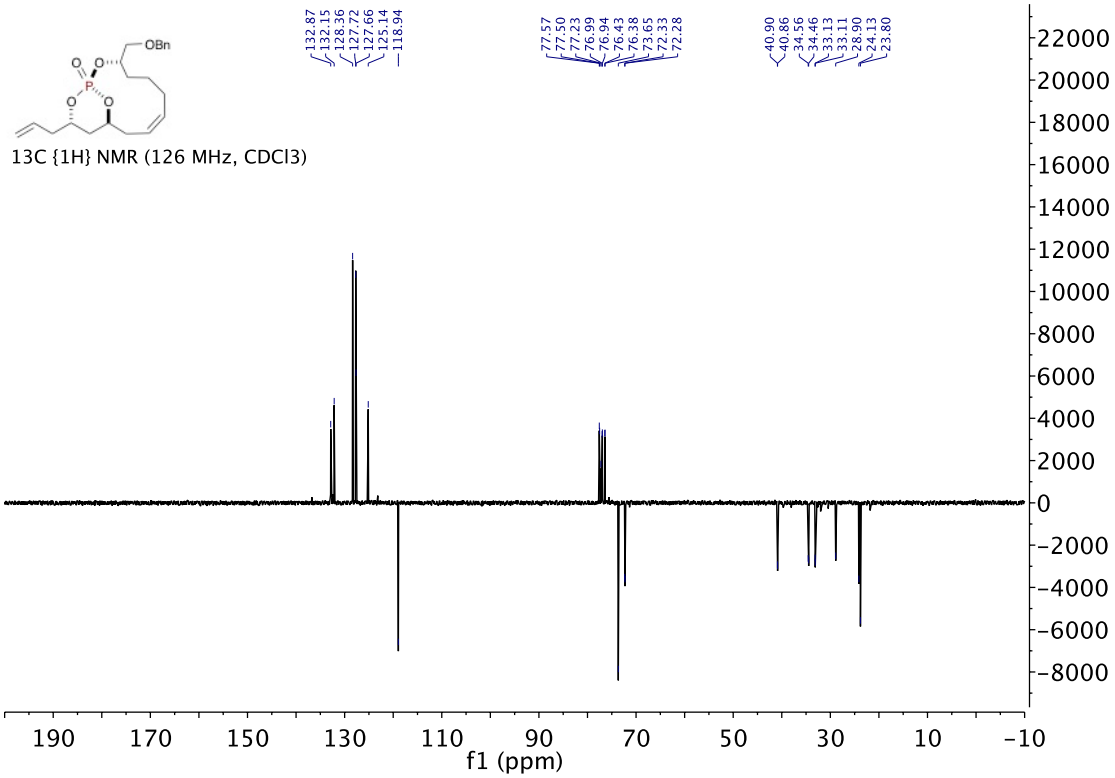

HSQC (CDCl3)
OBn
f2 (ppm)
f1 (ppm)

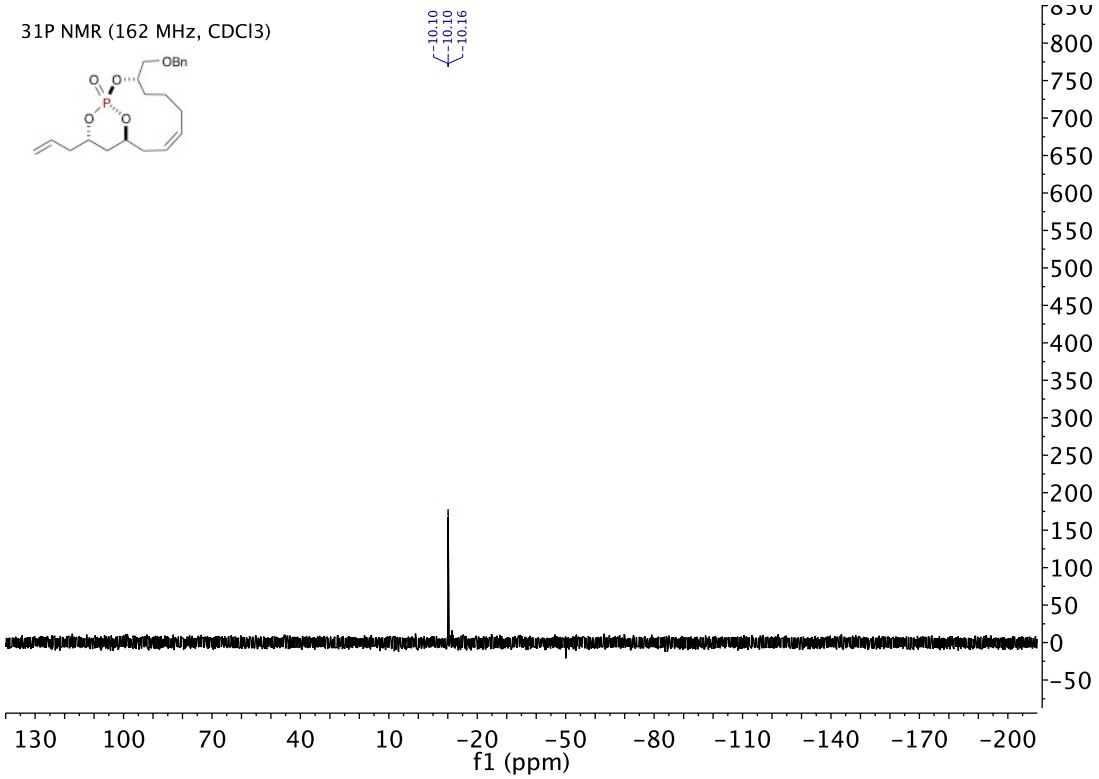
**(1*R*,3*S*,10*S*,12*S*,*Z*)-12-allyl-3-((benzyloxy)methyl)-2,13,14-trioxa-1-phosphabicyclo[8.3.1]tetradec-7-ene 1-oxide (*trans*-2.15.4)**

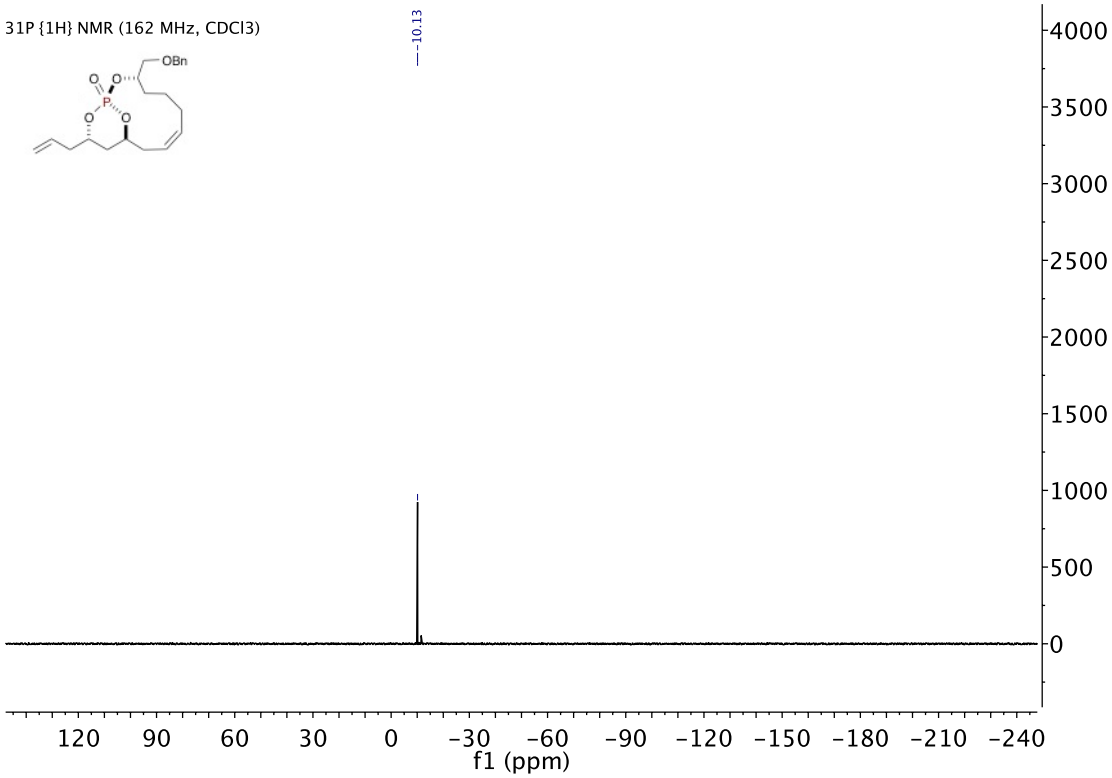


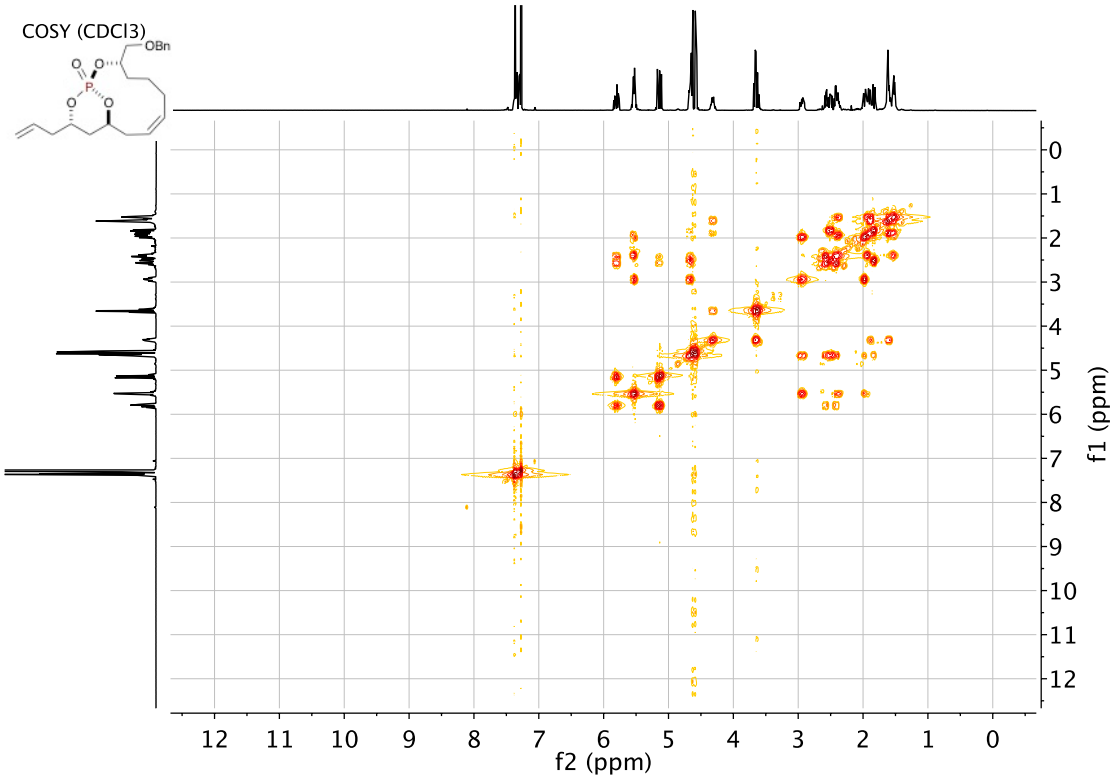



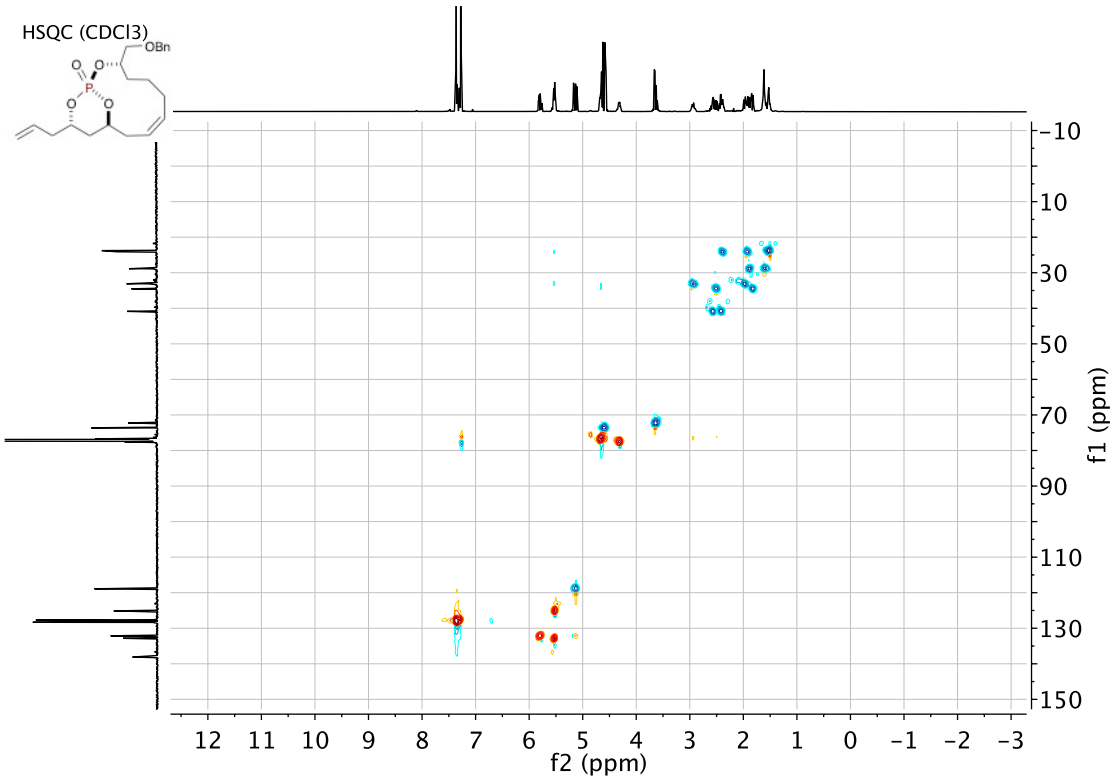

13C NMR (126 MHz, CDCl3)
OBn
138.10
132.83
132.12
128.33
127.69
127.63
125.11
118.91
77.54
77.47
77.25
77.00
77.00
76.96
76.91
76.75
76.40
76.35
73.62
72.30
72.25
40.87
40.83
34.53
34.43
33.10
33.08
28.87
24.10
23.77
f1 (ppm)

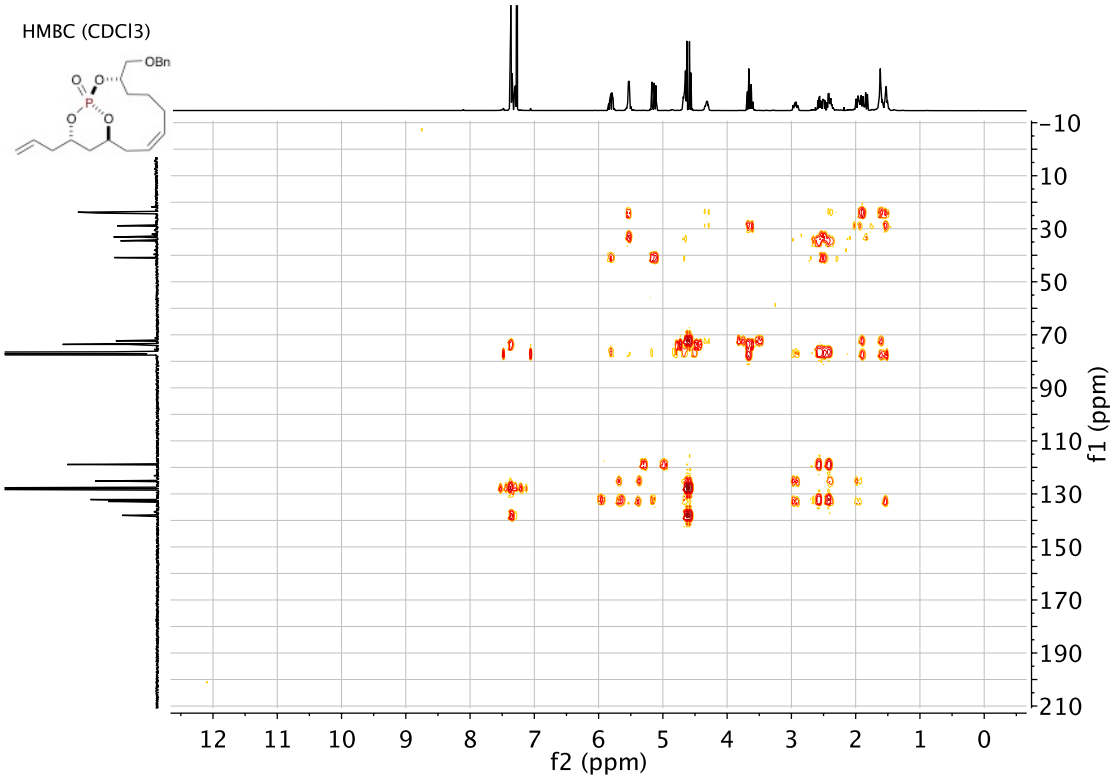

OBn
13C {1H} NMR (126 MHz, CDCl3)
132.87
132.15
128.36
127.72
127.66
125.14
118.94
77.57
77.50
77.23
76.99
76.94
76.43
76.38
73.65
72.33
72.28
40.90
40.86
34.56
34.46
33.13
33.11
28.90
24.13
23.80
f1 (ppm)

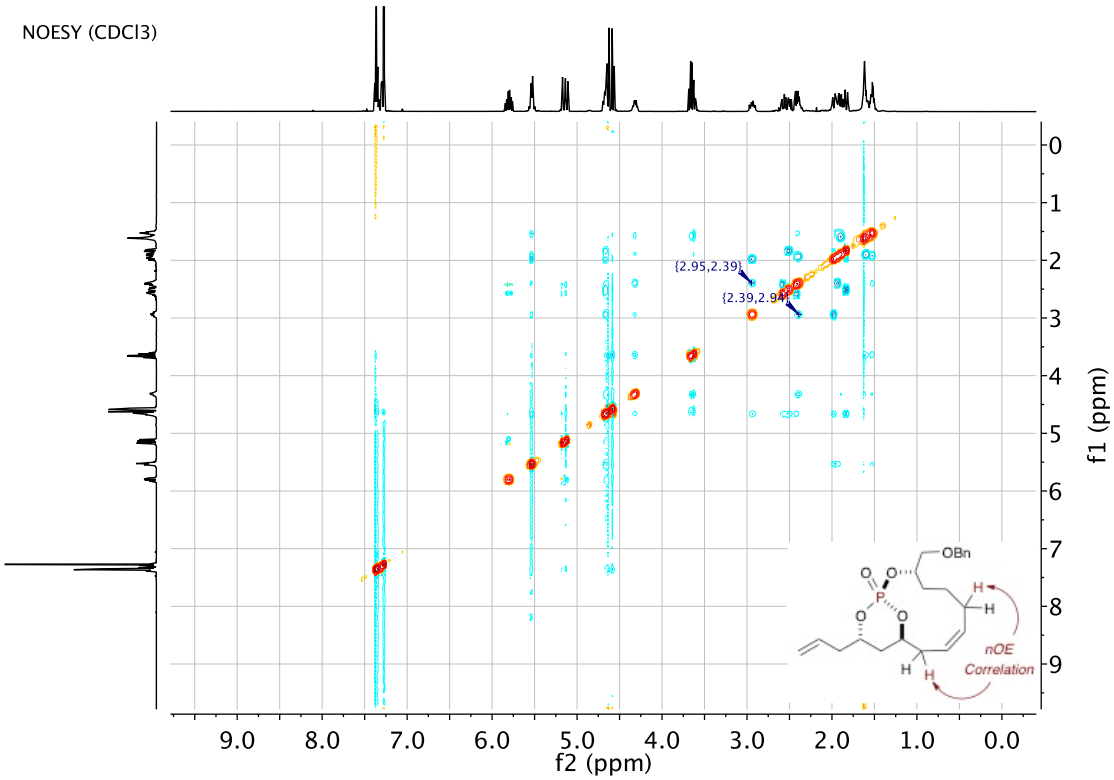

31P NMR (162 MHz, CDCl3)
OBn
10.10
10.10
10.16
800
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
130
100
70
40
10
-20
-50
-80
-110
-140
-170
-200
f1 (ppm)


31P {1H} NMR (162 MHz, CDCl3)
OBn
10.13
4000
3500
3000
2500
2000
1500
1000
500
0
120
90
60
30
0
-30
-60
-90
-120
-150
-180
-210
-240
f1 (ppm)

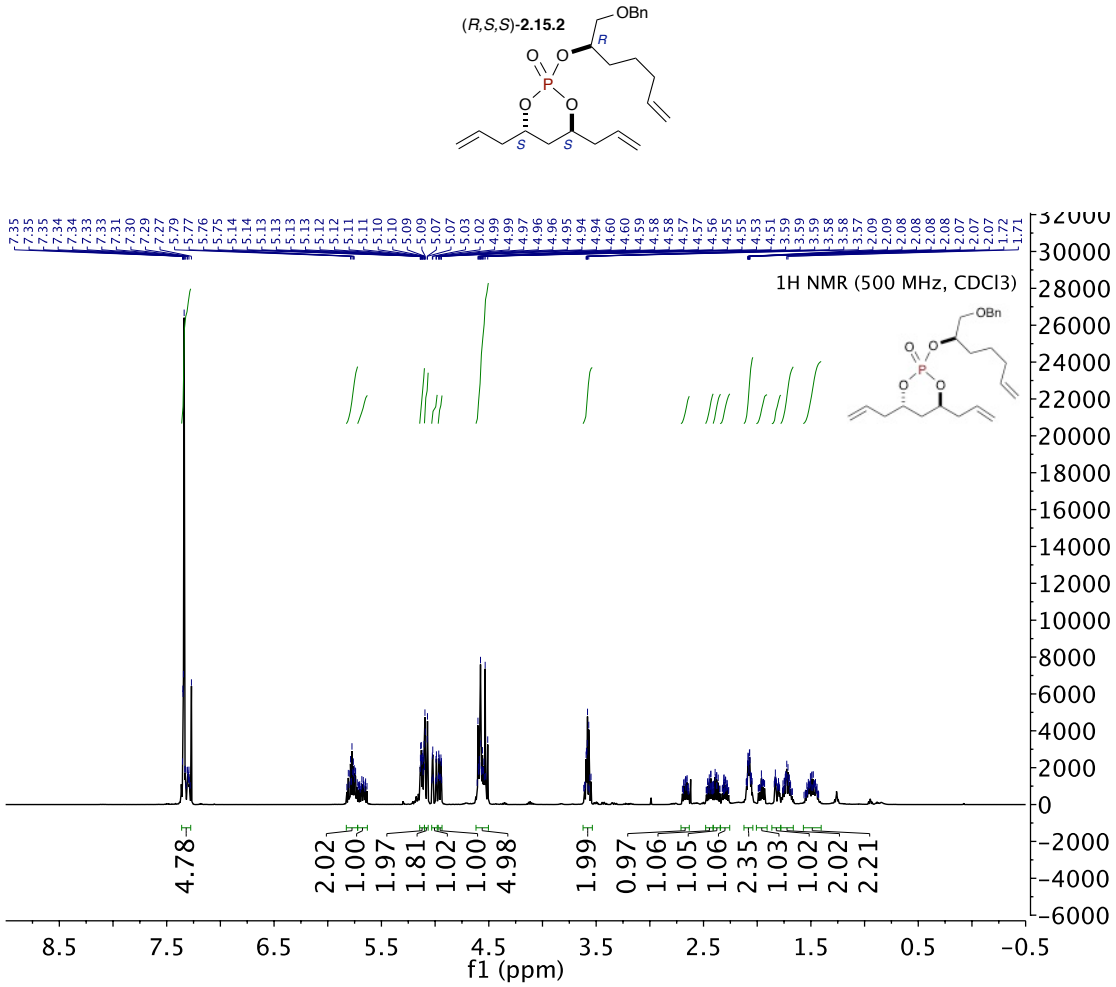

COSY (CDCl3)
OBn
f2 (ppm)
f1 (ppm)

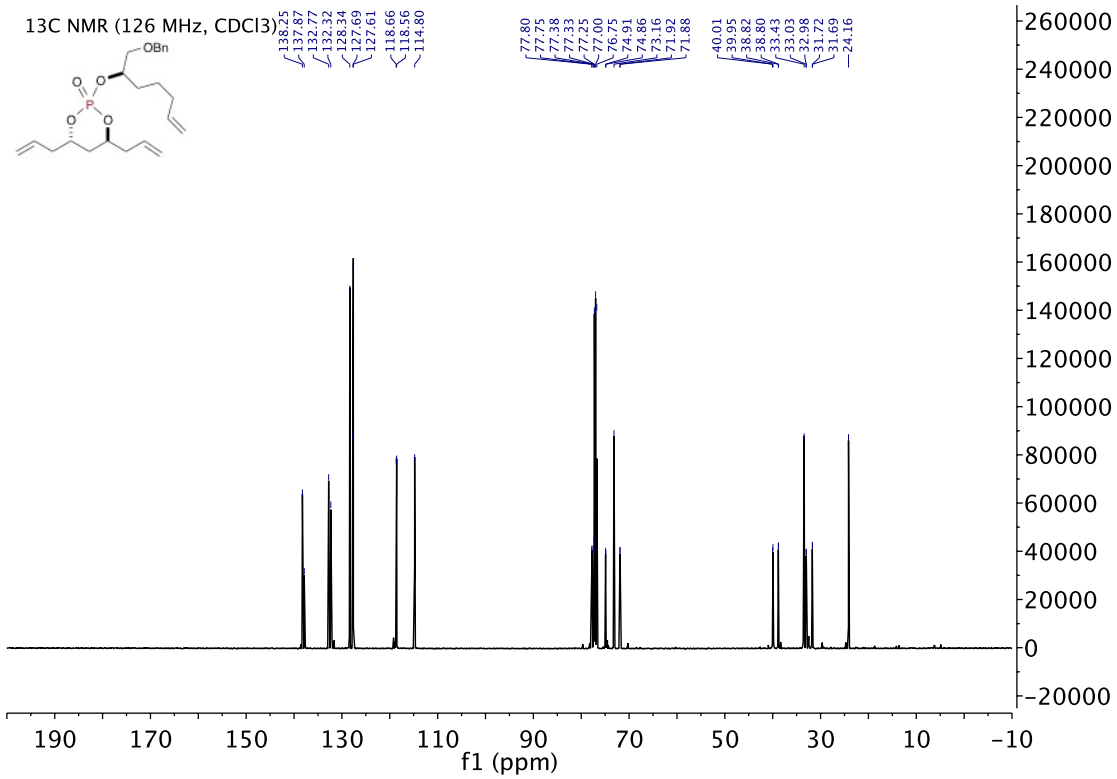

HSQC (CDCl3)
OBn
f2 (ppm)
f1 (ppm)

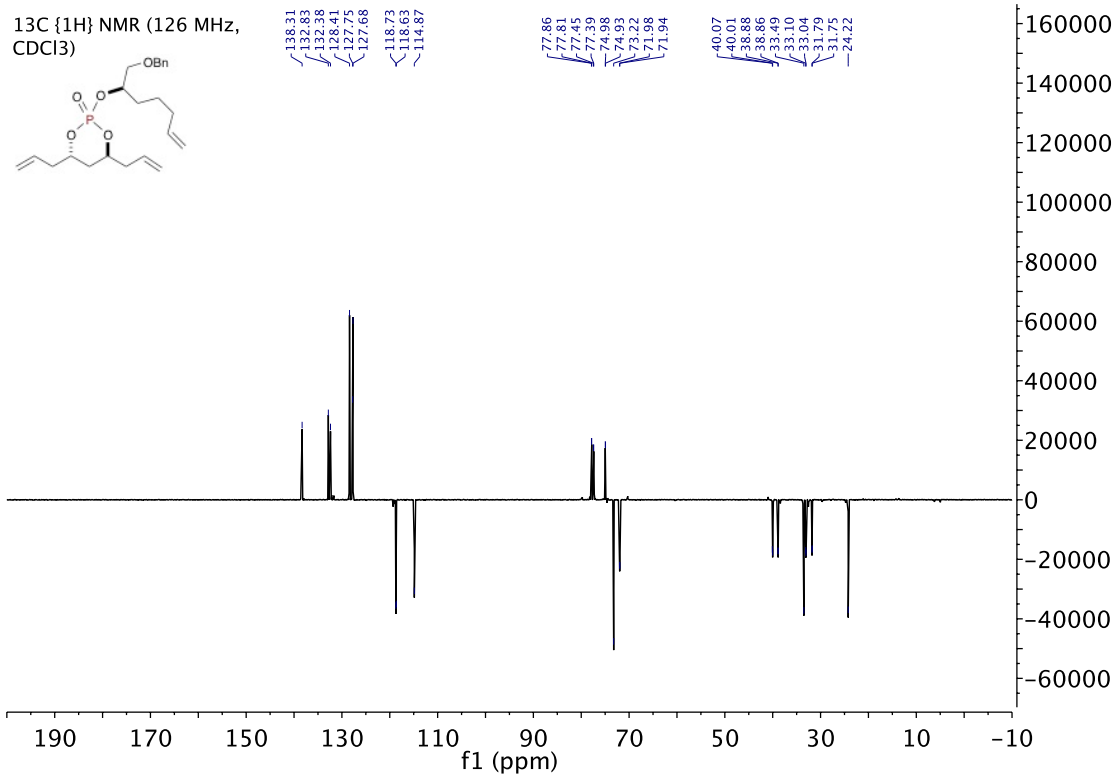

HMBC (CDCl3)
OBn
f2 (ppm)
f1 (ppm)

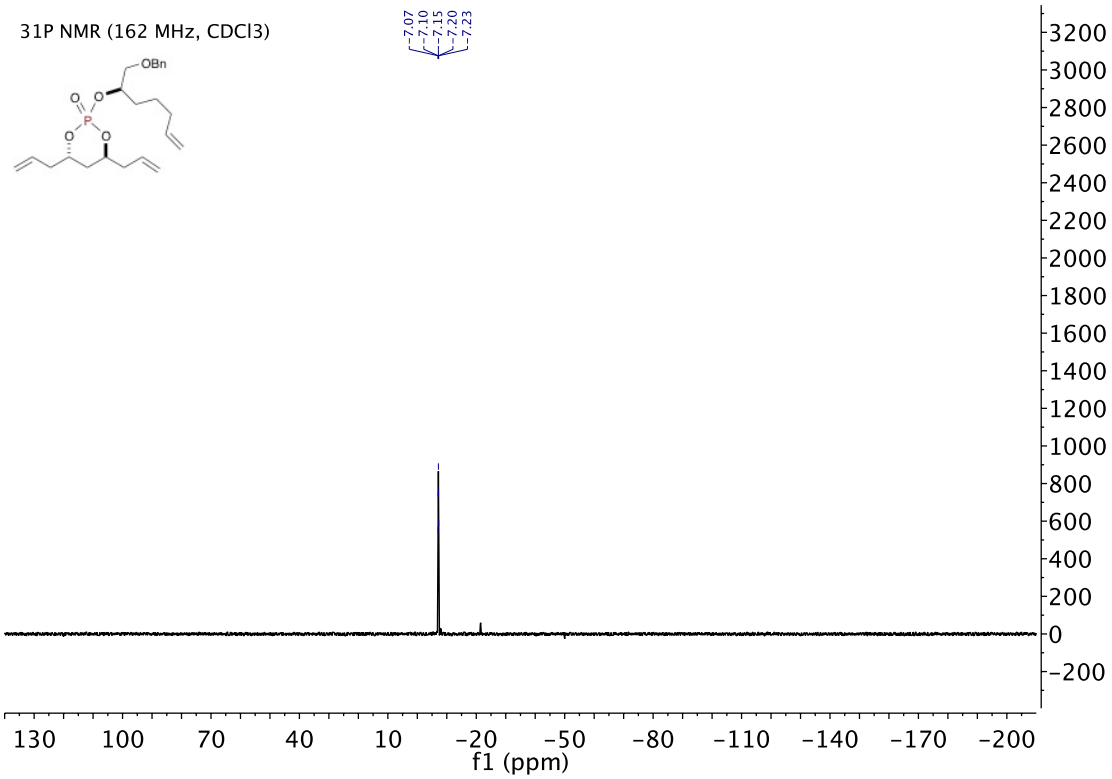

NOESY (CDCl3)
{2.95,2.39}
{2.39,2.94}
OBn
nOE
Correlation
f2 (ppm)
f1 (ppm)

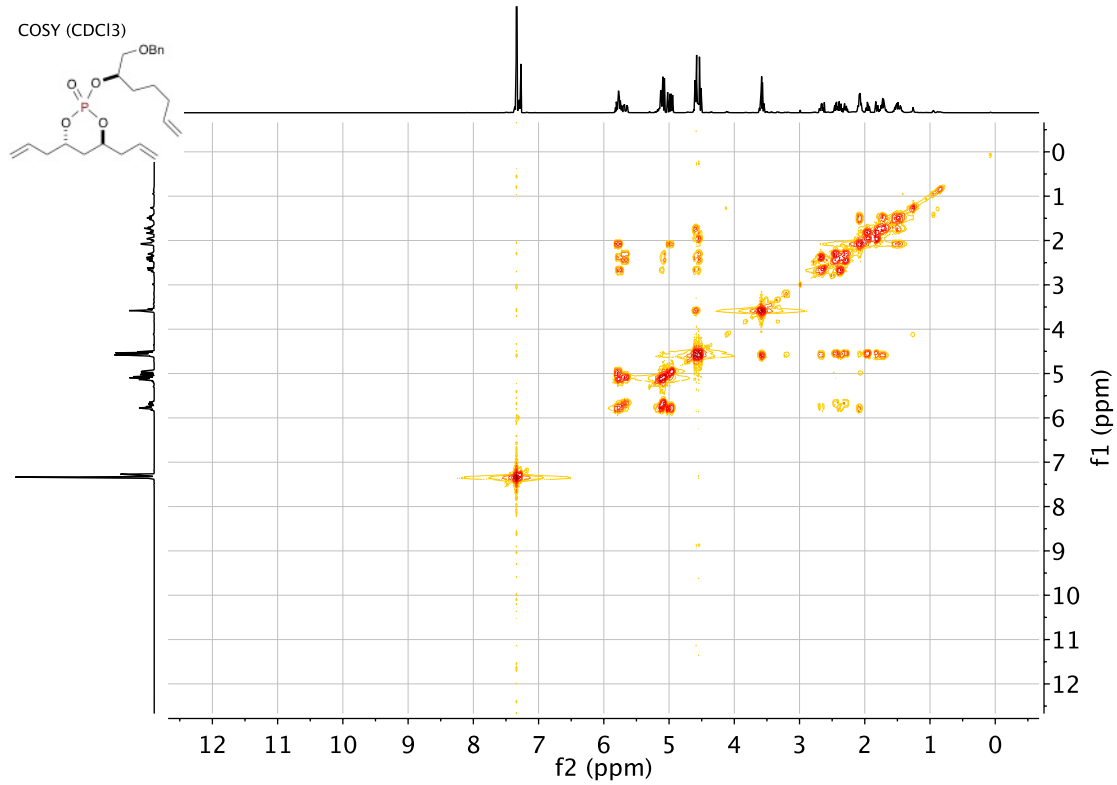
**(4*S*,6*S*)-4,6-diallyl-2-(((*R*)-1-(benzyloxy)hept-6-en-2-yl)oxy)-1,3,2-dioxaphosphinane 2-oxide (2.15.2)**

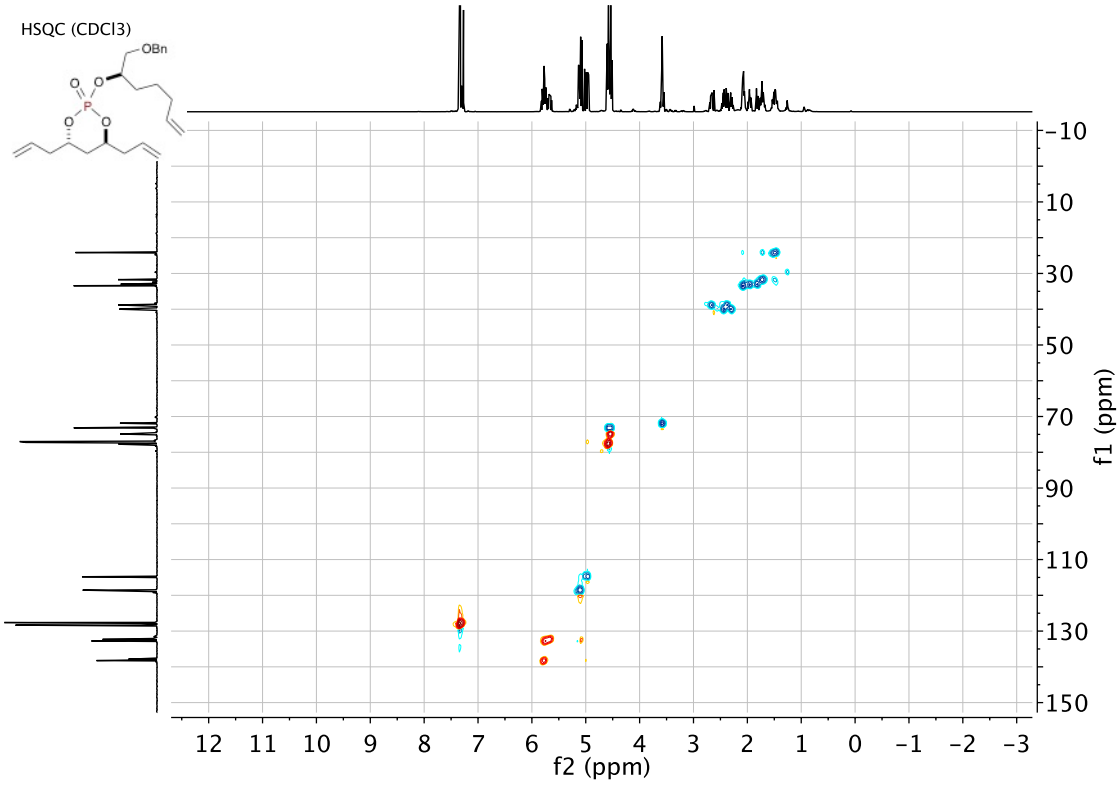



13C NMR (126 MHz, CDCl3)
OBn
138.25
137.87
132.77
132.32
128.34
127.69
127.61
118.66
118.56
114.80
77.80
77.75
77.38
77.33
77.25
77.00
76.75
74.91
74.86
73.16
71.92
71.88
40.01
39.95
38.82
38.80
33.43
33.03
32.98
31.72
31.69
24.16
260000
240000
220000
200000
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
-20000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

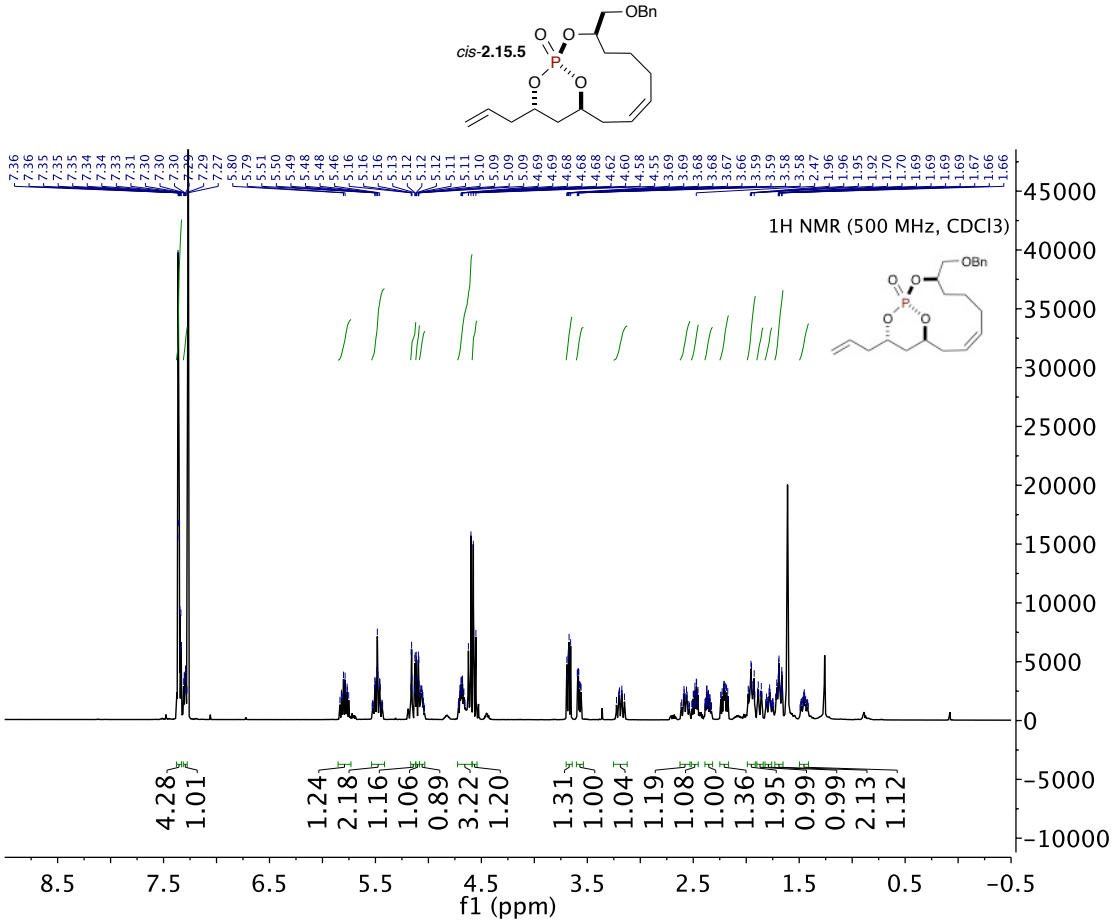

13C {1H} NMR (126 MHz, CDCl3)
OBn
138.31
132.83
132.38
128.41
127.75
127.68
118.73
118.63
114.87
77.86
77.81
77.45
77.39
74.98
74.93
73.22
71.98
71.94
40.07
40.01
38.88
38.86
33.49
33.10
33.04
31.79
31.75
24.22
160000
140000
120000
100000
80000
60000
40000
20000
0
-20000
-40000
-60000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

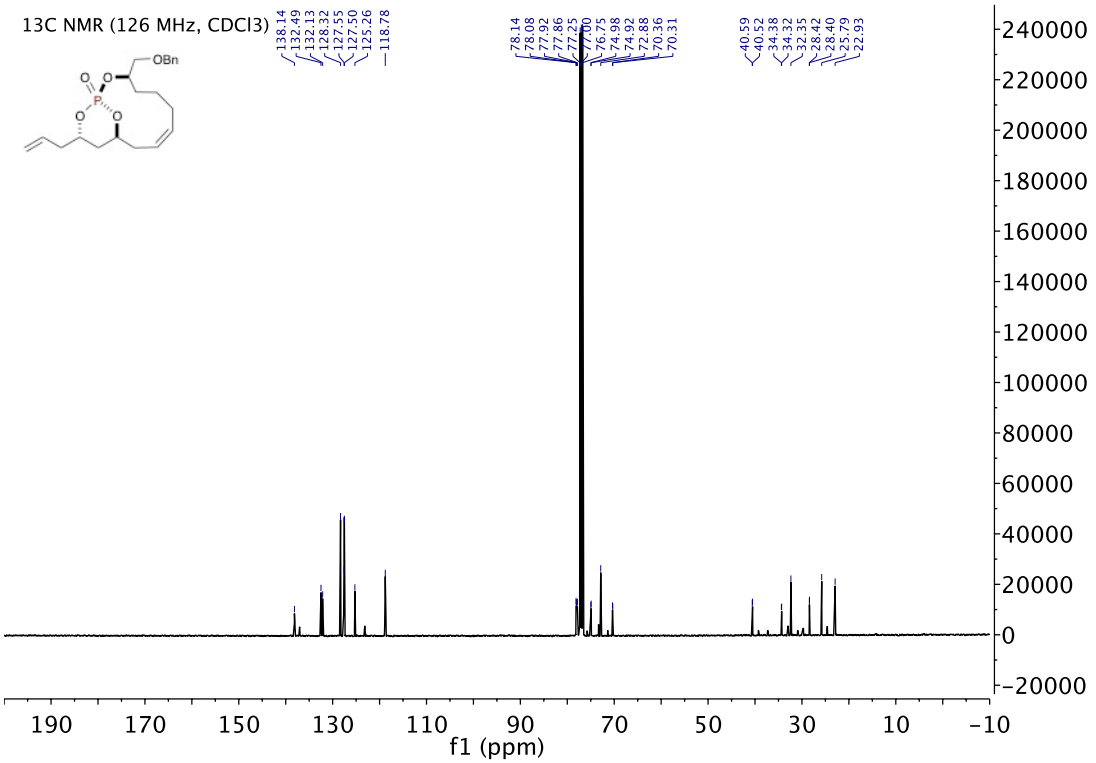

31P NMR (162 MHz, CDCl3)
OBn
7.07
7.10
7.15
7.20
7.23
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
130
100
70
40
10
-20
-50
-80
-110
-140
-170
-200
f1 (ppm)

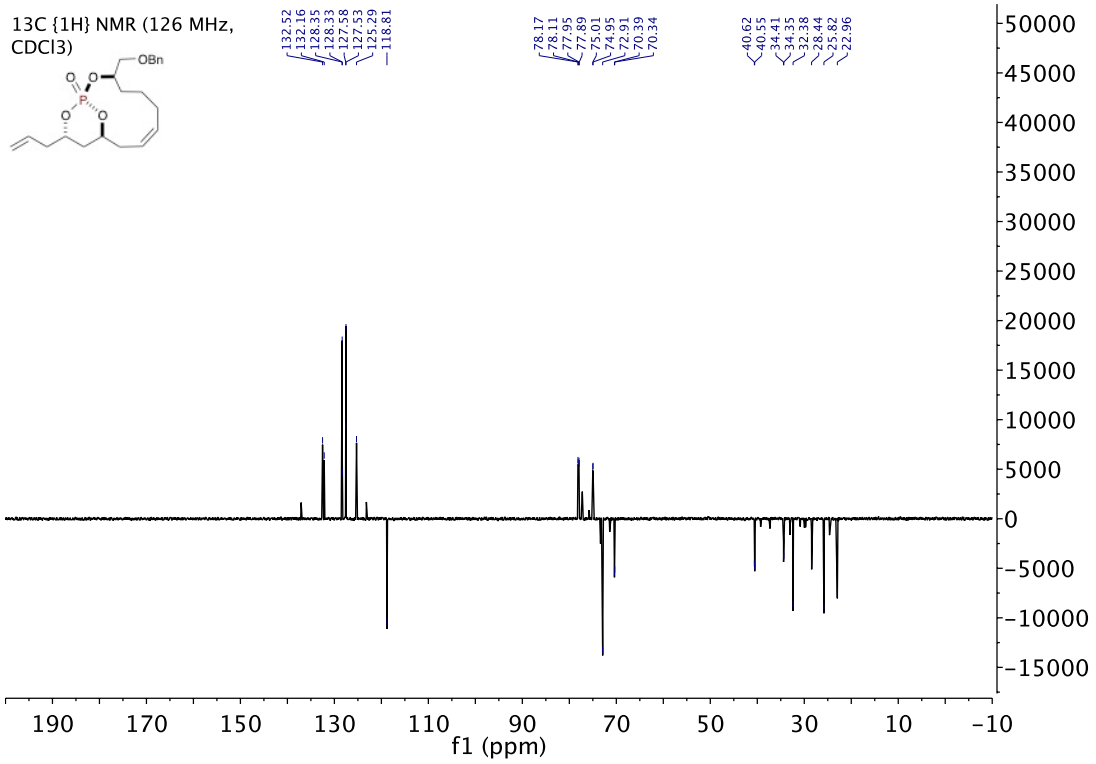

COSY (CDCl3)
OBn
0
1
2
3
4
5
6
7
8
9
10
11
12
f1 (ppm)
12
11
10
9
8
7
6
5
4
3
2
1
0
f2 (ppm)

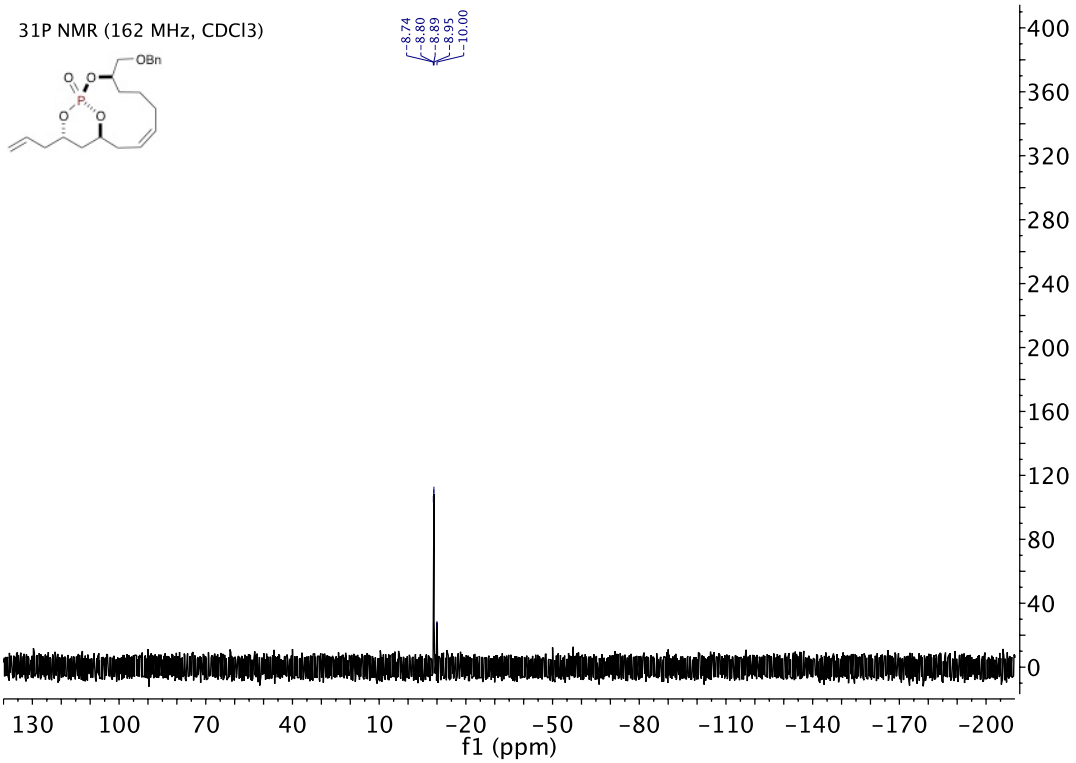

HSQC (CDCl3)
OBn
O
O
P
O
O
12
11
10
9
8
7
6
5
4
3
2
1
0
−1
−2
−3
f2 (ppm)
−10
10
30
50
70
90
110
130
150
f1 (ppm)

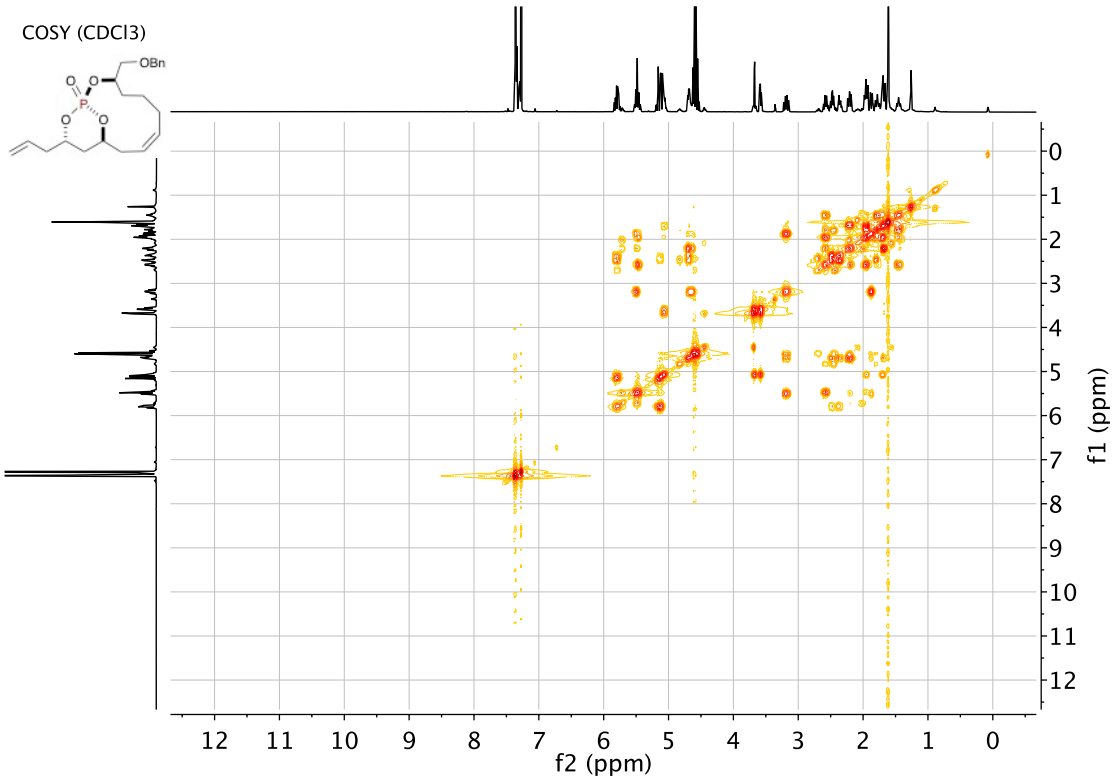
**(1*R*,3*R*,10*S*,12*S*,*Z*)-12-allyl-3-((benzyloxy)methyl)-2,13,14-trioxa-1-phosphabicyclo[8.3.1]tetradec-7-ene 1-oxide (*cis*-2.15.5**, major pdt**)**

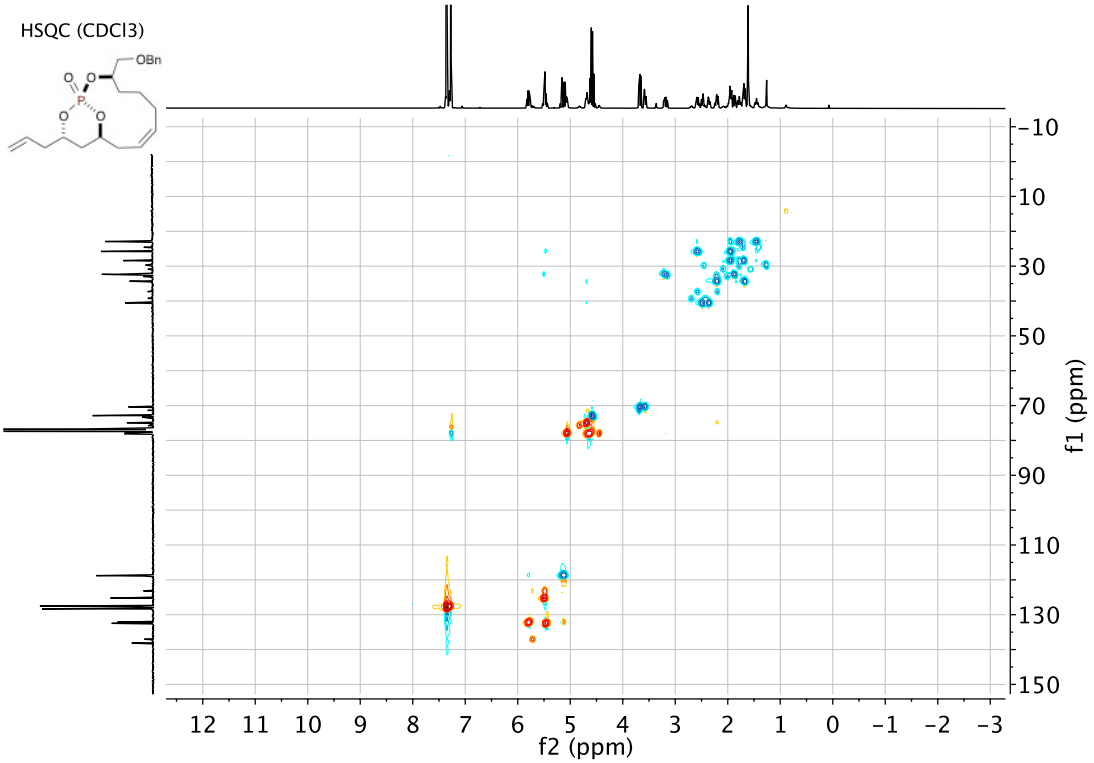


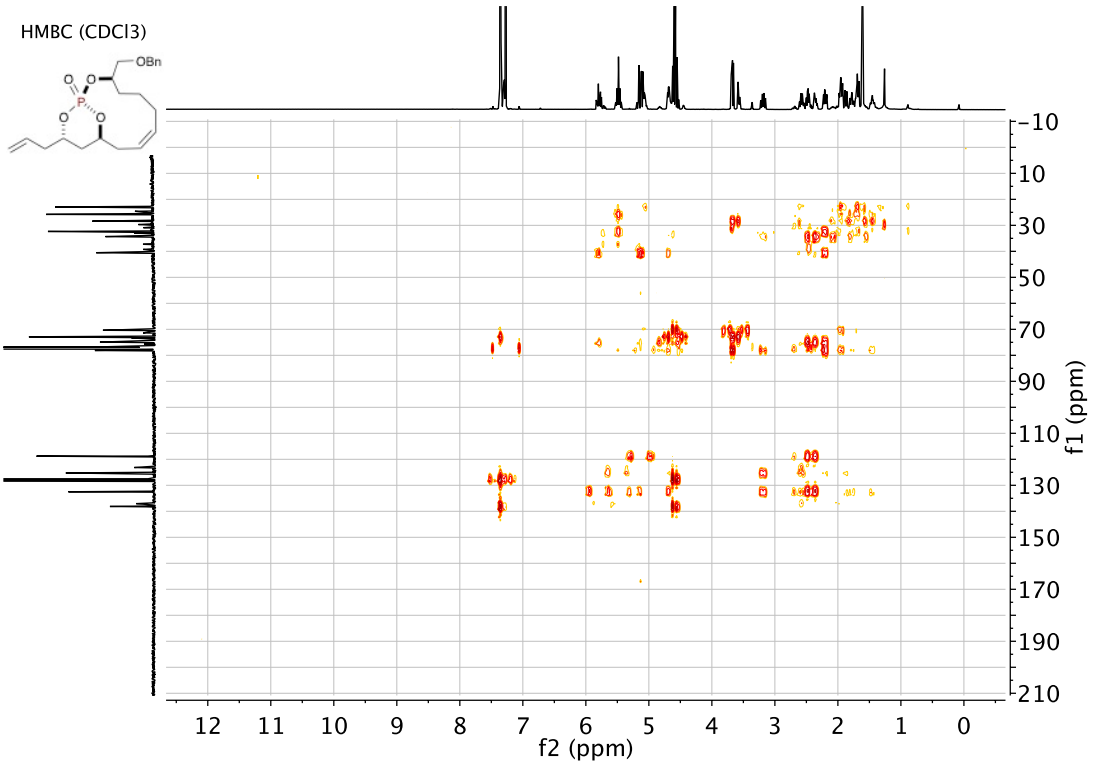

13C NMR (126 MHz, CDCl3)
OBn
138.14
132.49
132.13
128.32
127.55
127.50
125.26
118.78
78.14
78.08
77.92
77.86
77.25
77.00
76.75
74.98
74.92
72.88
70.36
70.31
40.59
40.52
34.38
34.32
32.35
28.42
28.40
25.79
22.93
240000
220000
200000
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
-20000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

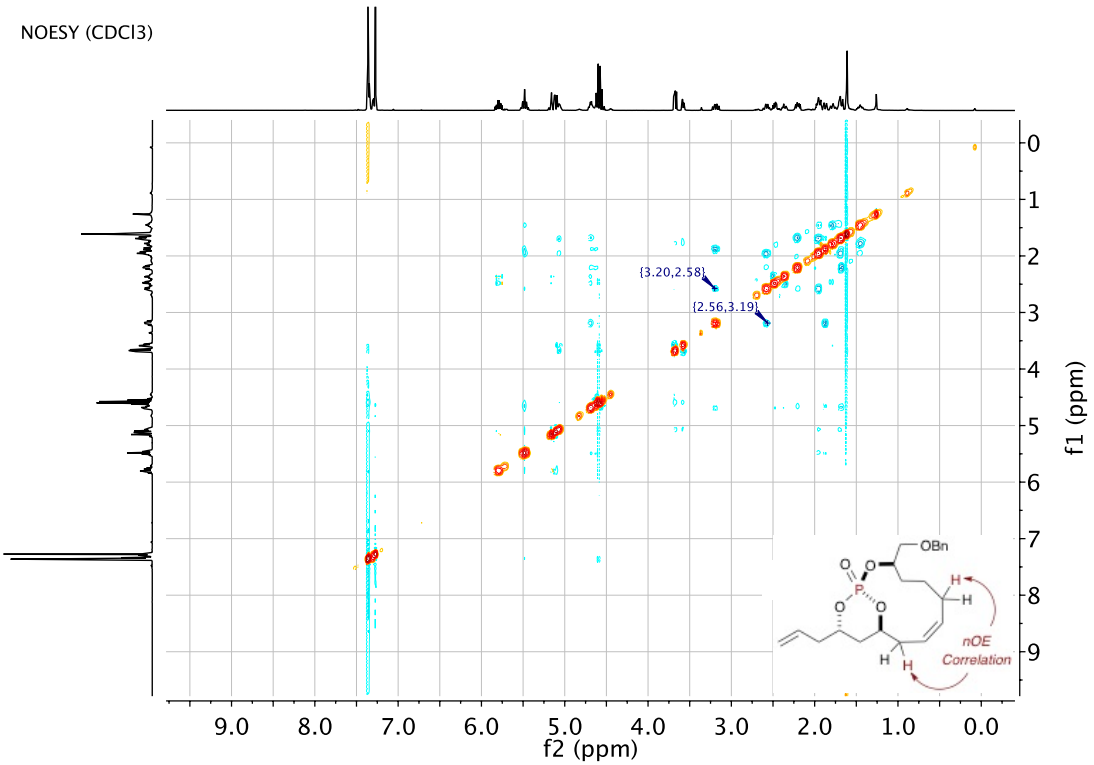

13C {1H} NMR (126 MHz, CDCl3)
OBn
132.52
132.16
128.35
128.33
127.58
127.53
125.29
118.81
78.17
78.11
77.95
77.89
75.01
74.95
72.91
70.39
70.34
40.62
40.55
34.41
34.35
32.38
28.44
25.82
22.96
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
-10000
-15000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)


31P NMR (162 MHz, CDCl3)
OBn
8.74
8.80
8.89
8.95
10.00
400
360
320
280
240
200
160
120
80
40
0
130
100
70
40
10
-20
-50
-80
-110
-140
-170
-200
f1 (ppm)

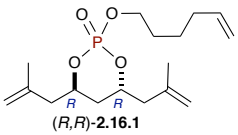

COSY (CDCl3)
OBn
0
1
2
3
4
5
6
7
8
9
10
11
12
f1 (ppm)
12
11
10
9
8
7
6
5
4
3
2
1
0
f2 (ppm)


HSQC (CDCl3)
OBn
12 11 10 9 8 7 6 5 4 3 2 1 0 −1 −2 −3
f2 (ppm)
−10 10 30 50 70 90 110 130 150
f1 (ppm)

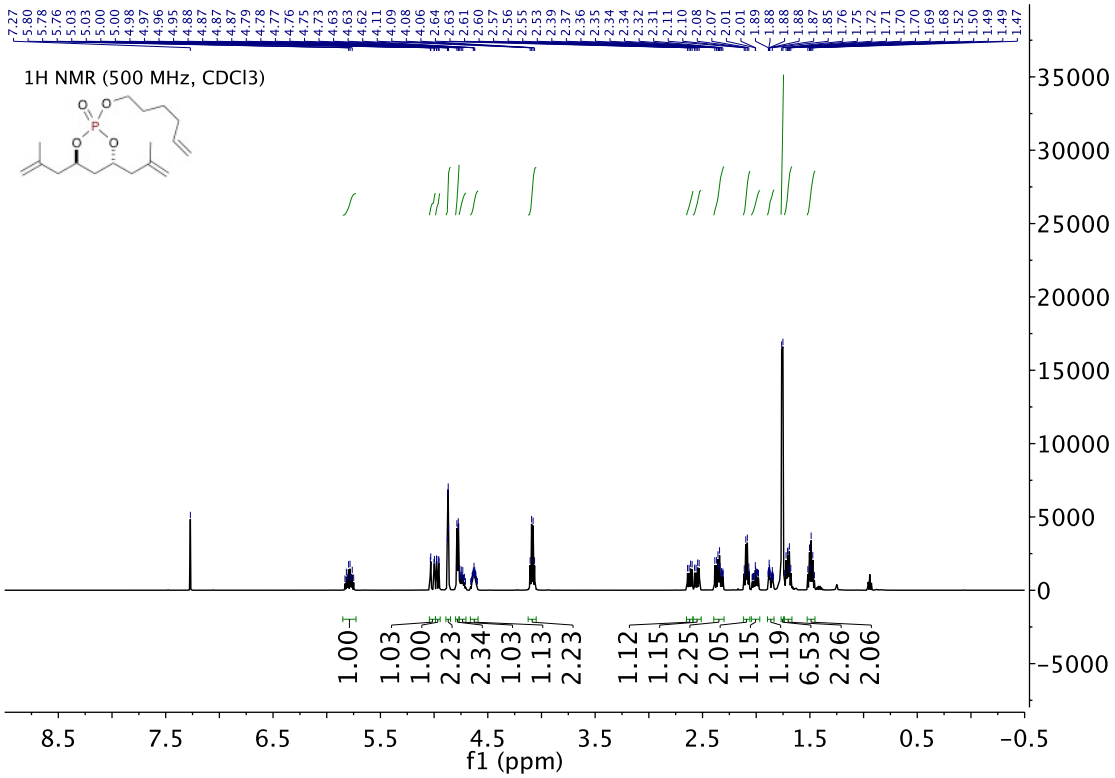

HMBC (CDCl3)
OBn
12 11 10 9 8 7 6 5 4 3 2 1 0
f2 (ppm)
−10 10 30 50 70 90 110 130 150 170 190 210
f1 (ppm)

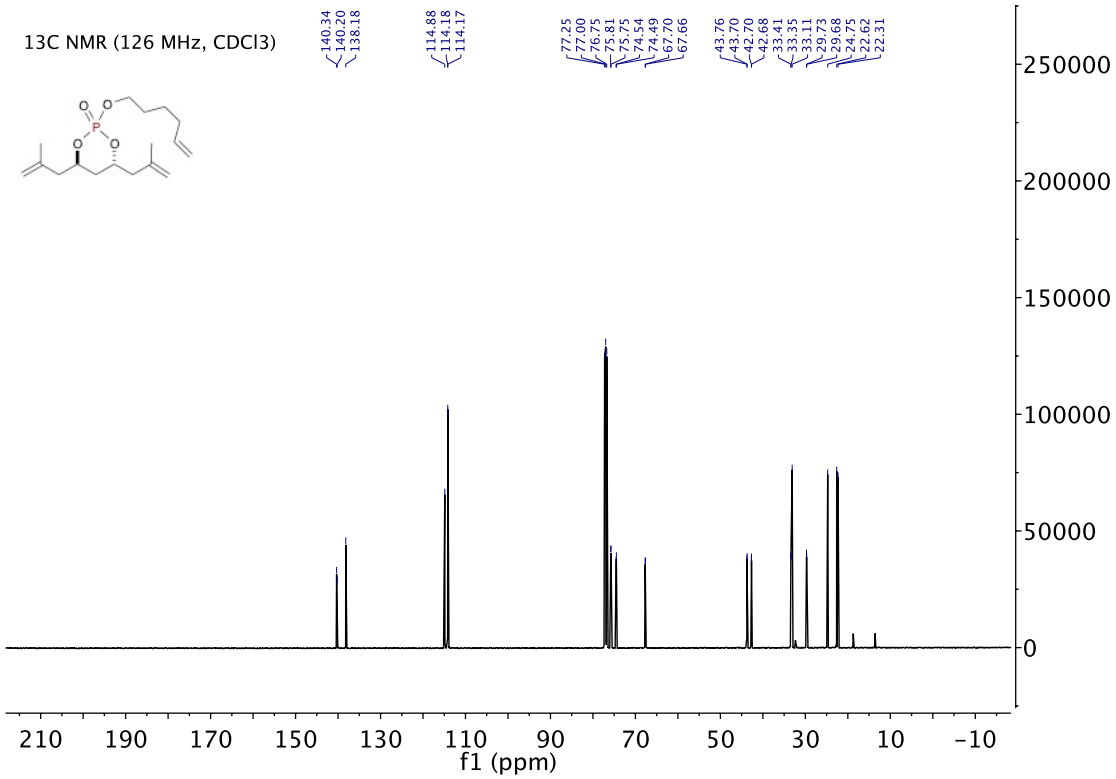

NOESY (CDCl3)
{3.20,2.58}
{2.56,3.19}
OBn
nOE
Correlation
f2 (ppm)
f1 (ppm)

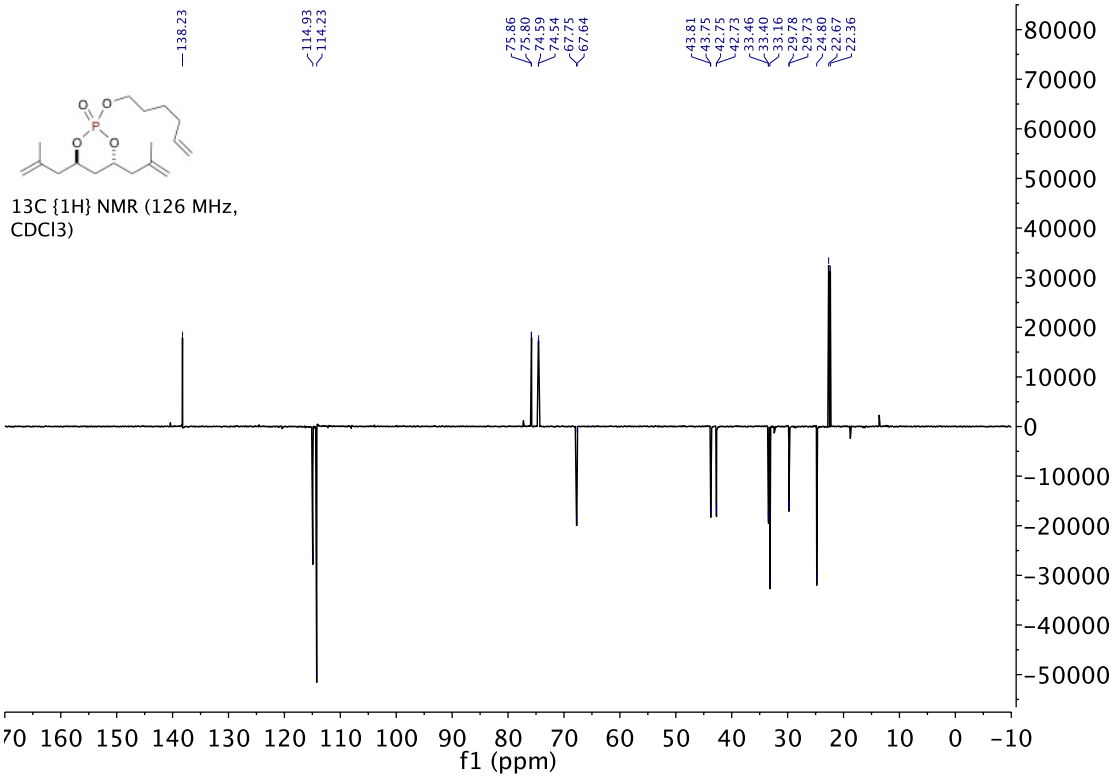
**(4*R*,6*R*)-2-(hex-5-en-1-yloxy)-4,6-bis(2-methylallyl)-1,3,2-dioxaphosphinane 2-oxide (2.16.1)**

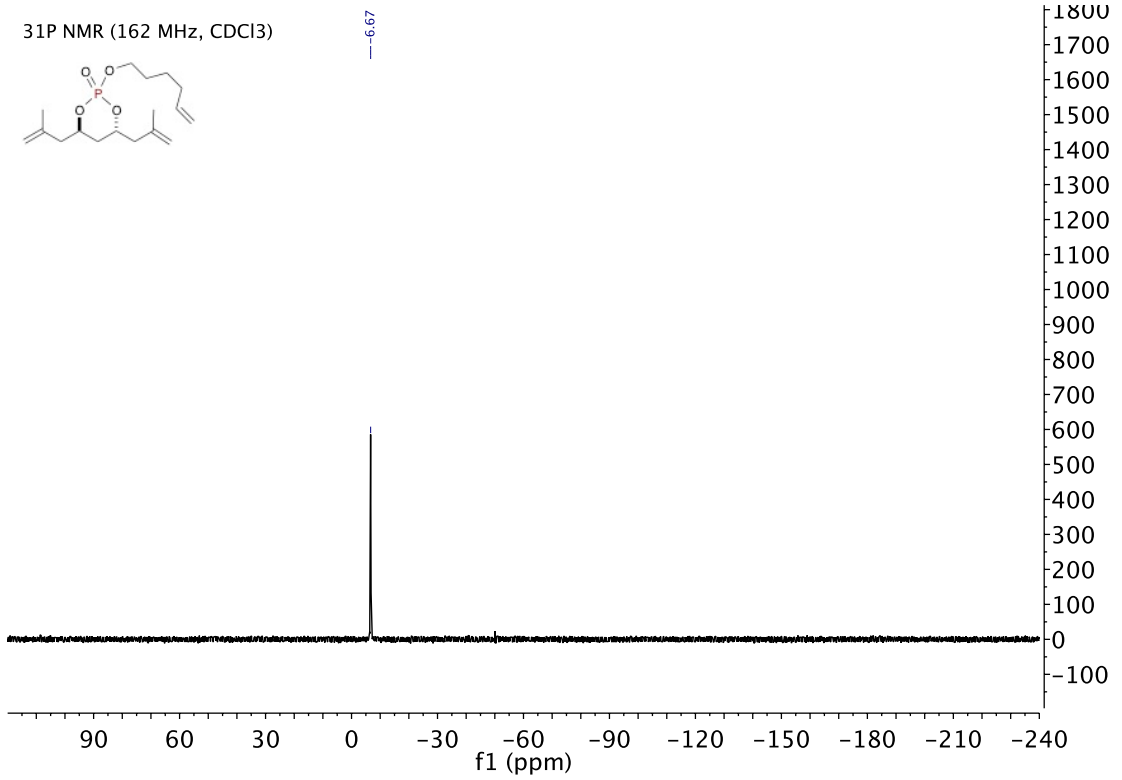


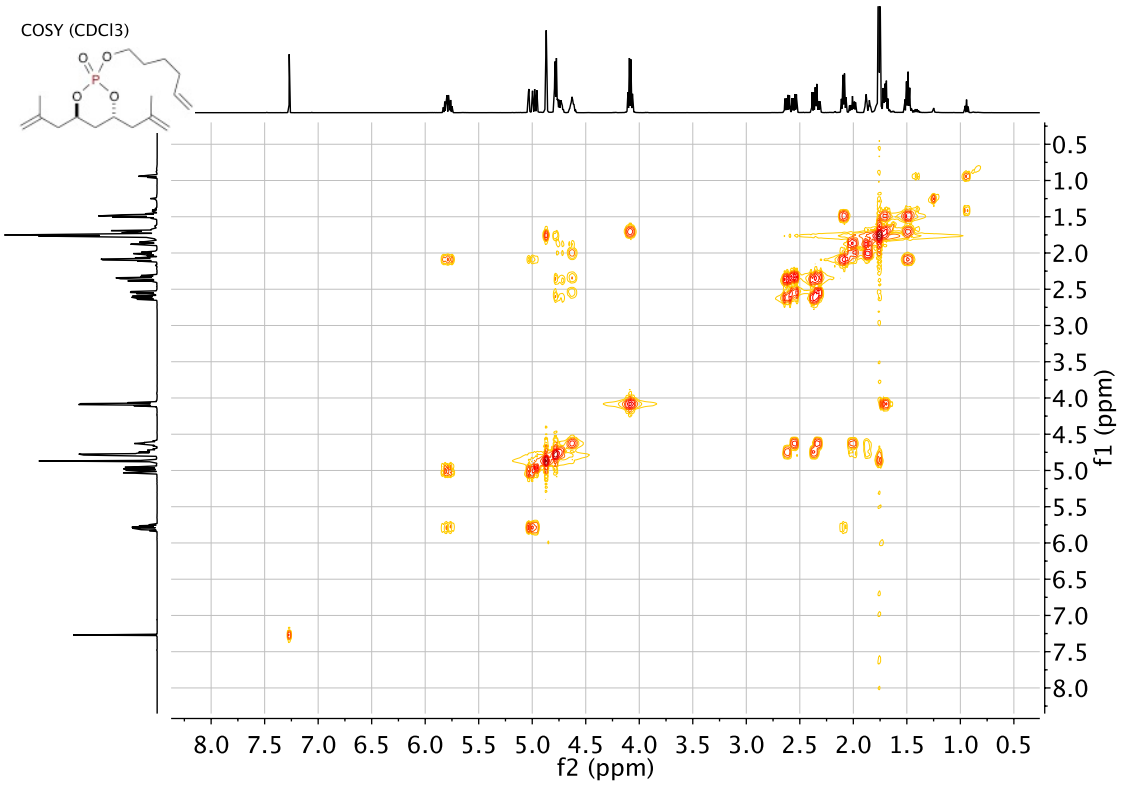

(*R*,*R*)-**2.16.1**

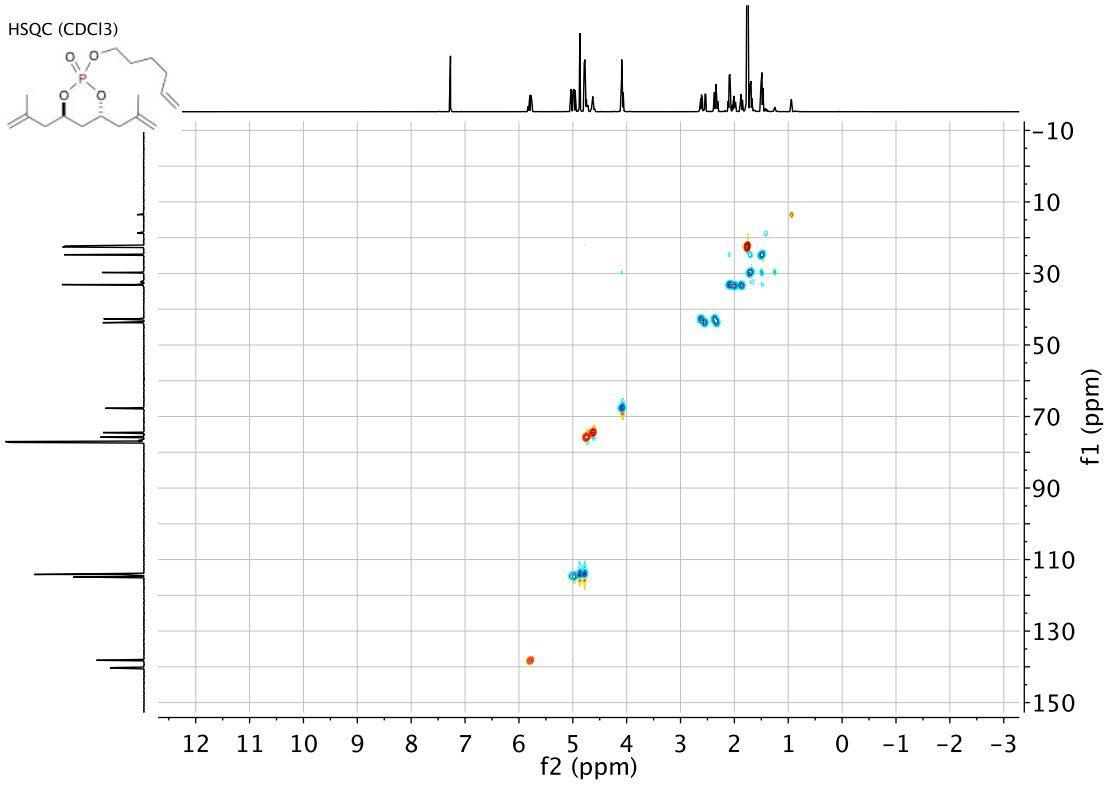



13C NMR (126 MHz, CDCl3)
140.34
140.20
138.18
114.88
114.18
114.17
77.25
77.00
76.75
75.81
75.75
74.54
74.49
67.70
67.66
43.76
43.70
42.70
42.68
33.41
33.35
33.11
29.73
29.68
24.75
22.62
22.31
250000
200000
150000
100000
50000
0
210 190 170 150 130 110 90 70 50 30 10 -10
f1 (ppm)

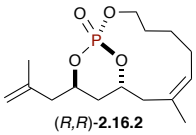

138.23
114.93
114.23
75.86
75.80
74.59
74.54
67.75
67.64
43.81
43.75
42.75
42.73
33.46
33.40
33.16
29.78
29.73
24.80
22.67
22.36
13C {1H} NMR (126 MHz, CDCl3)
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
-20000
-30000
-40000
-50000
70 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

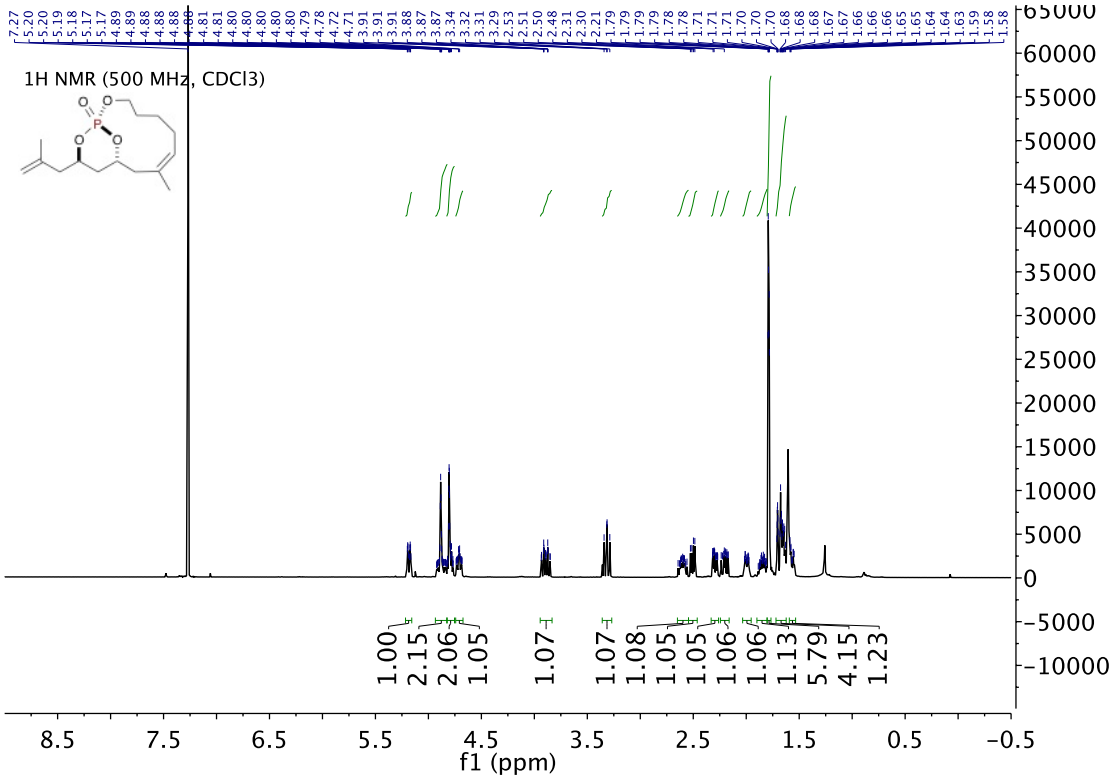

31P NMR (162 MHz, CDCl3)
-6.67
f1 (ppm)

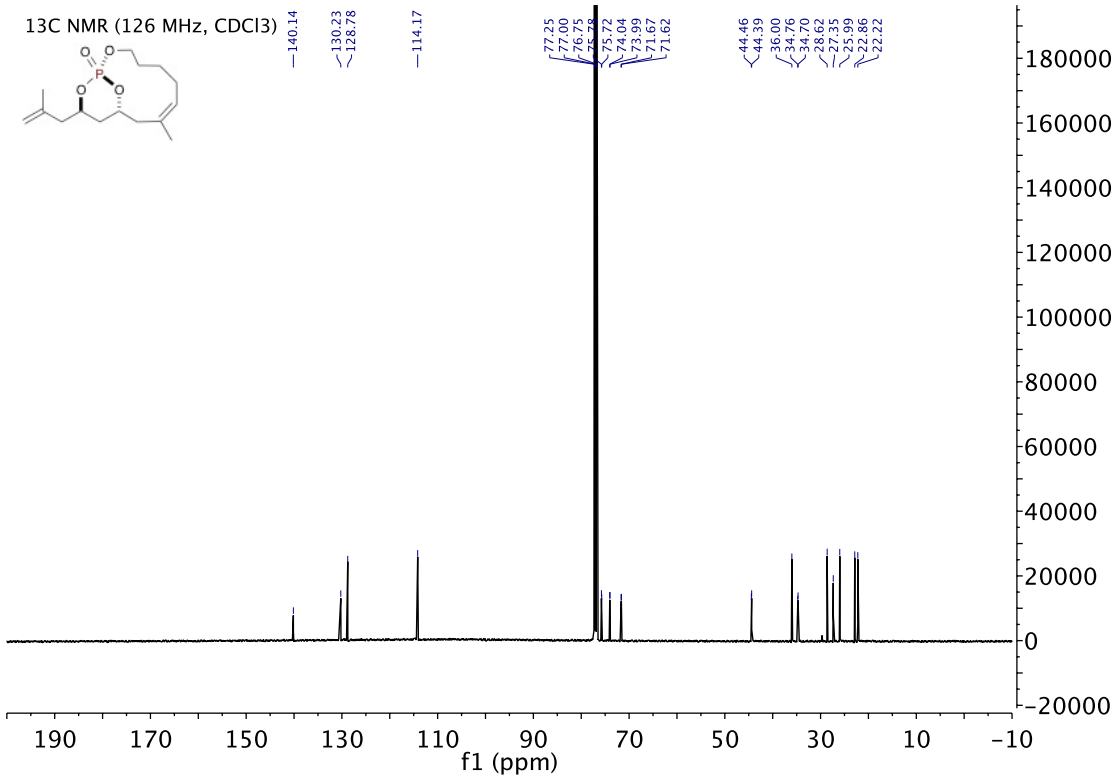

COSY (CDCl3)
f2 (ppm)
f1 (ppm)

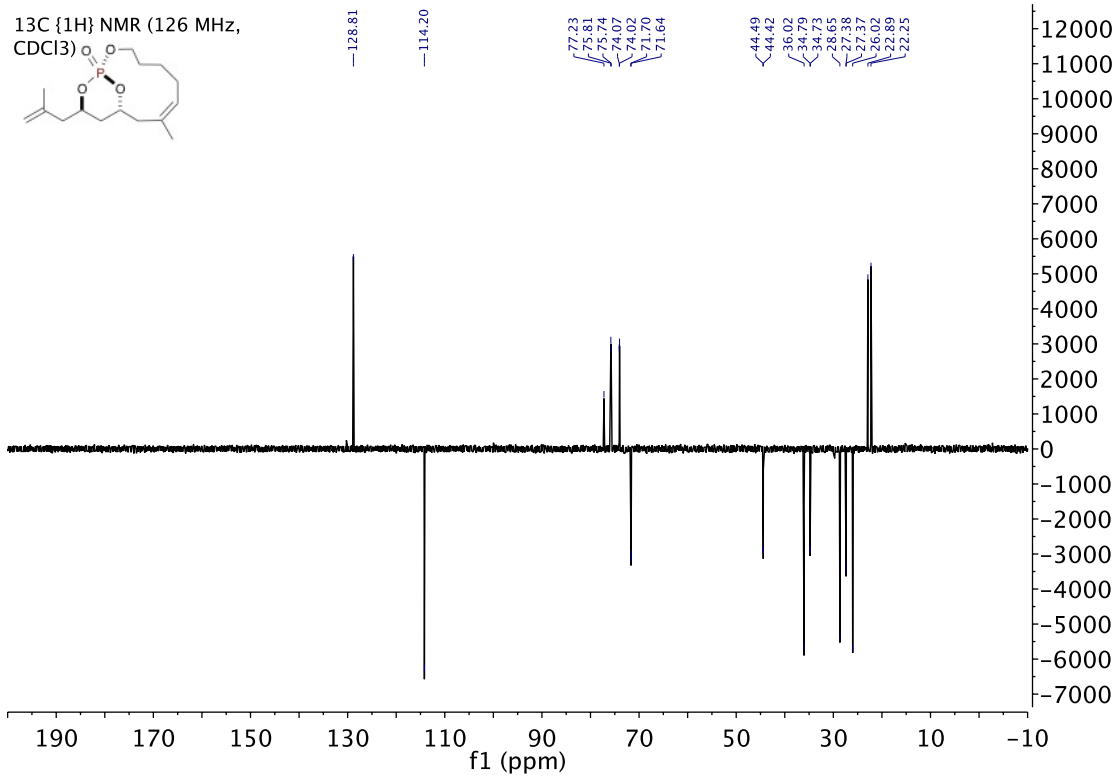

HSQC (CDCl3)
f2 (ppm)
f1 (ppm)

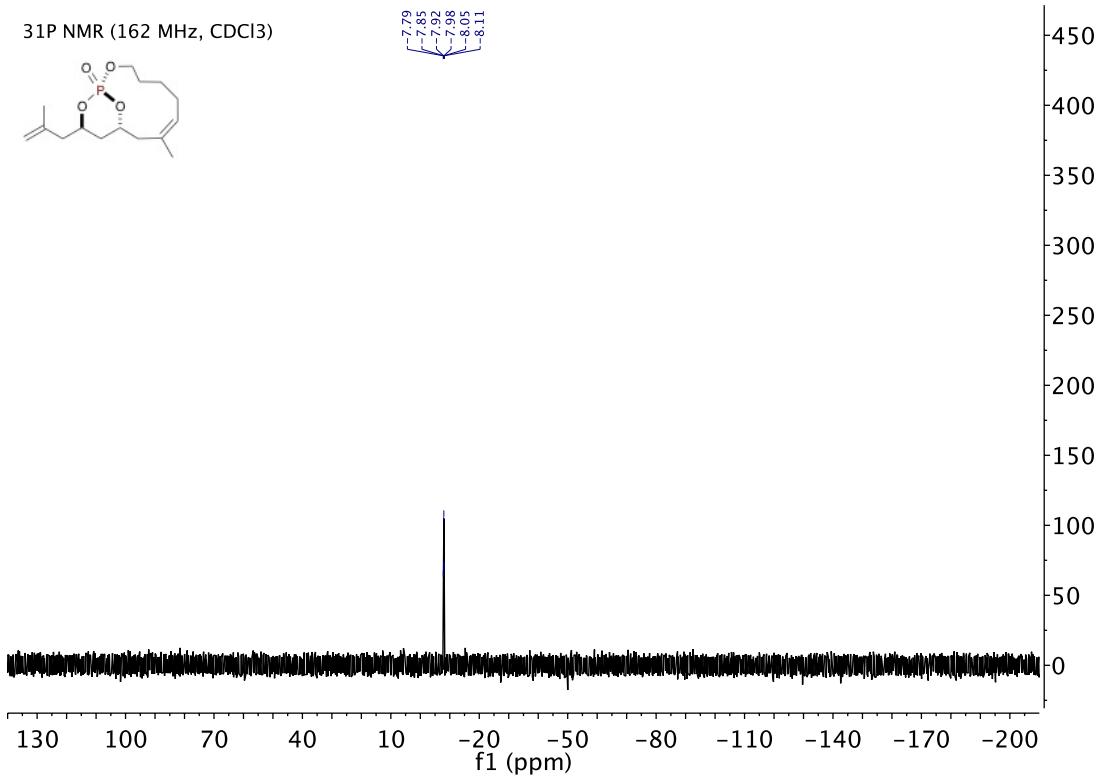
**(1*S*,10*R*,12*R*,*Z*)-8-methyl-12-(2-methylallyl)-2,13,14-trioxa-1-phosphabicyclo[8.3.1]tetradec-7-ene 1-oxide (2.16.2)**

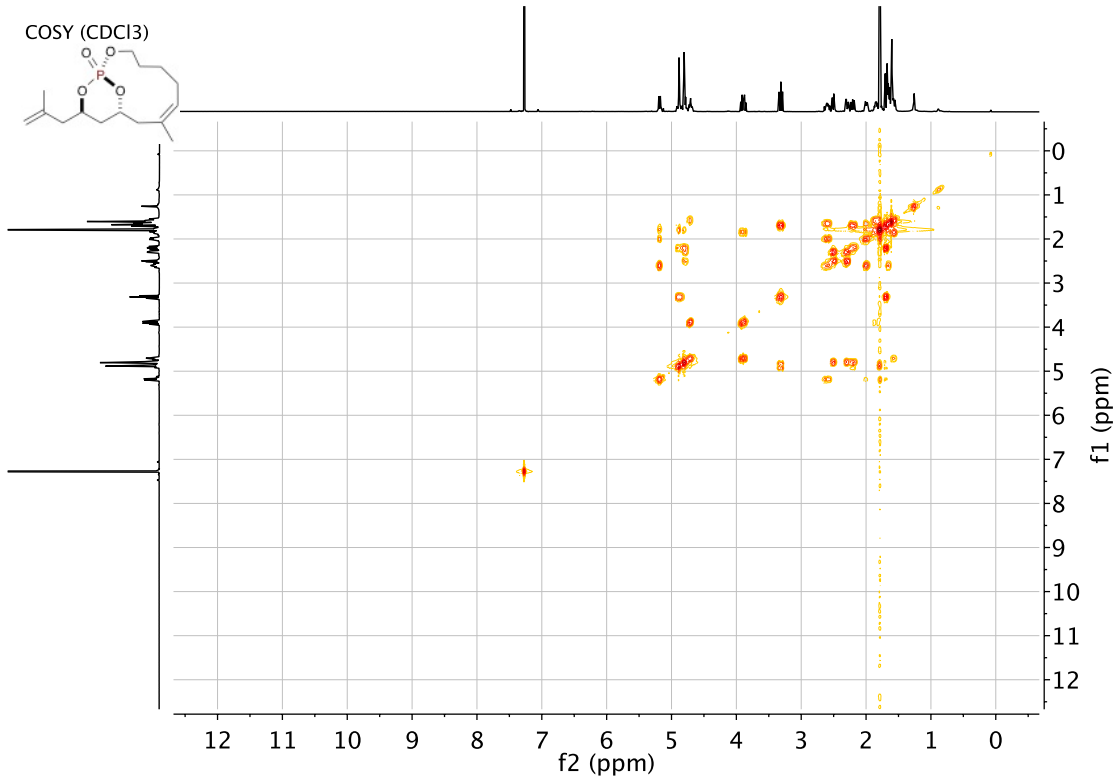


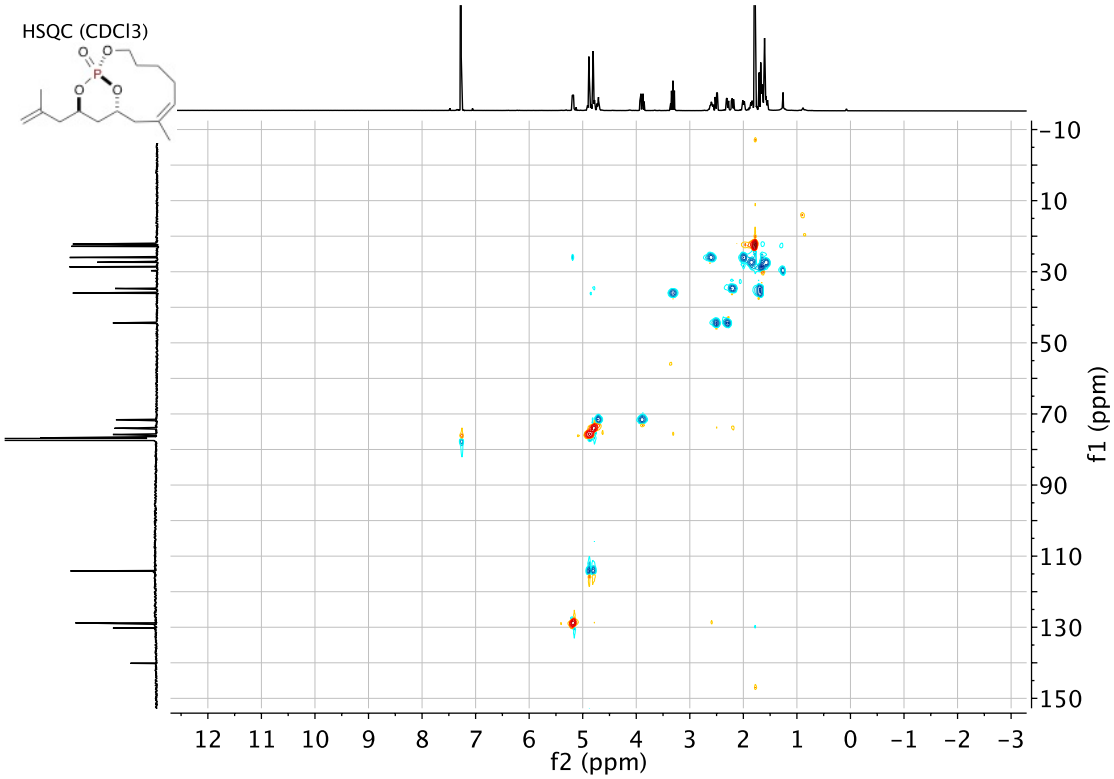



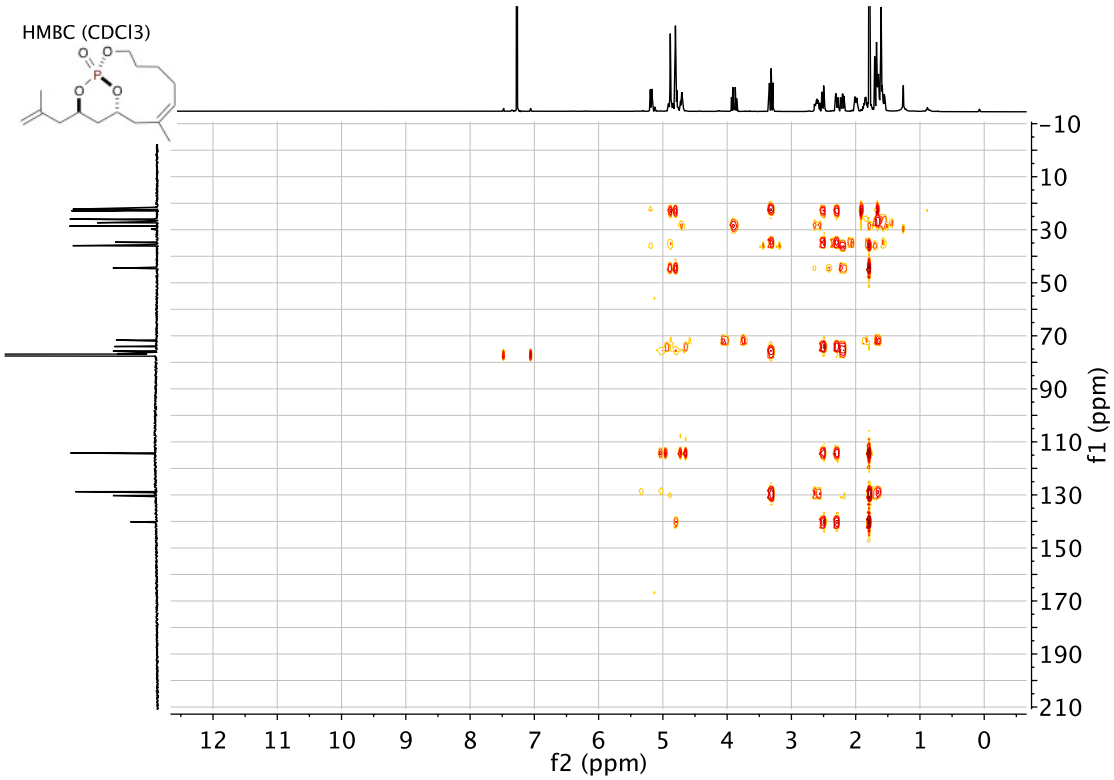

13C NMR (126 MHz, CDCl3)
140.14
130.23
128.78
114.17
77.25
77.00
76.75
75.72
74.04
73.99
71.67
71.62
44.46
44.39
36.00
34.76
34.70
28.62
27.35
25.99
22.86
22.22
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
-20000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

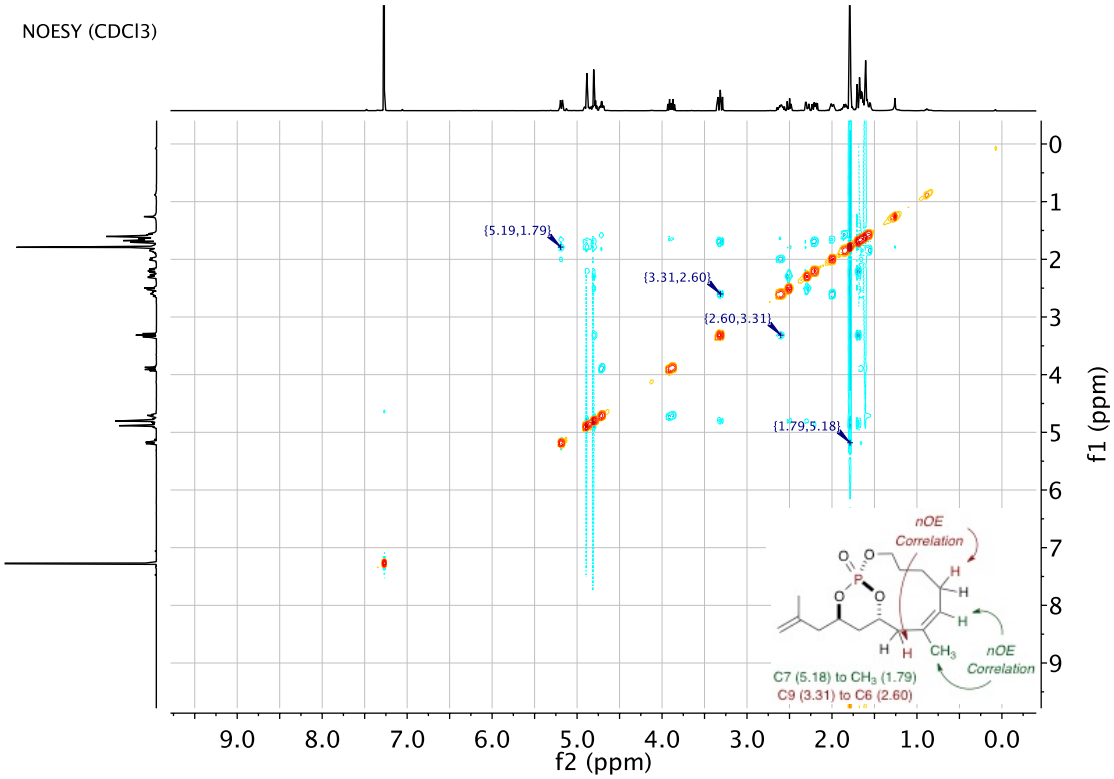

13C {1H} NMR (126 MHz, CDCl3)
128.81
114.20
77.23
75.81
75.74
74.07
74.02
71.70
71.64
44.49
44.42
36.02
34.79
34.73
28.65
27.38
27.37
26.02
22.89
22.25
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-2000
-3000
-4000
-5000
-6000
-7000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)


31P NMR (162 MHz, CDCl3)
7.79
7.85
7.92
7.98
8.05
8.11
450
400
350
300
250
200
150
100
50
0
130
100
70
40
10
-20
-50
-80
-110
-140
-170
-200
f1 (ppm)

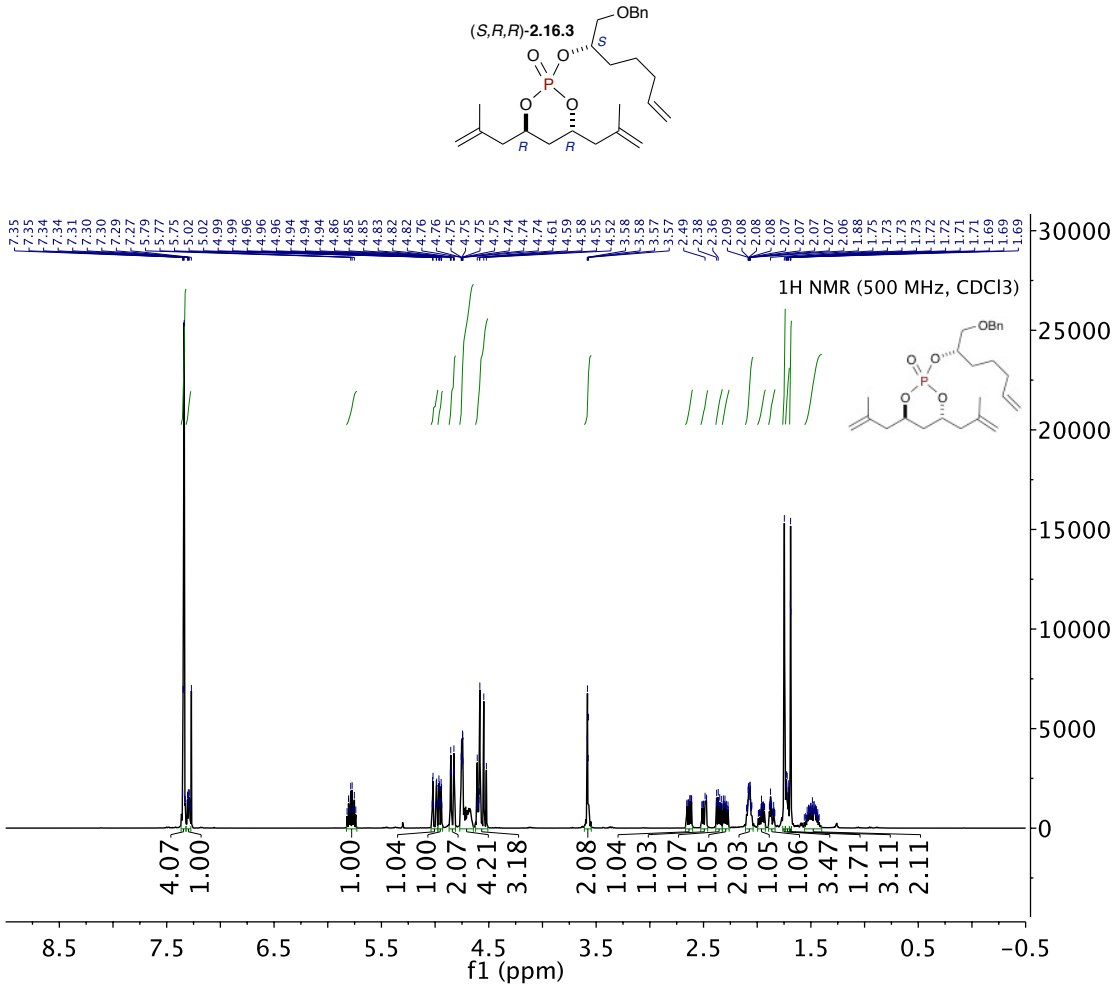

COSY (CDCl3)
0
1
2
3
4
5
6
7
8
9
10
11
12
f1 (ppm)
12
11
10
9
8
7
6
5
4
3
2
1
0
f2 (ppm)

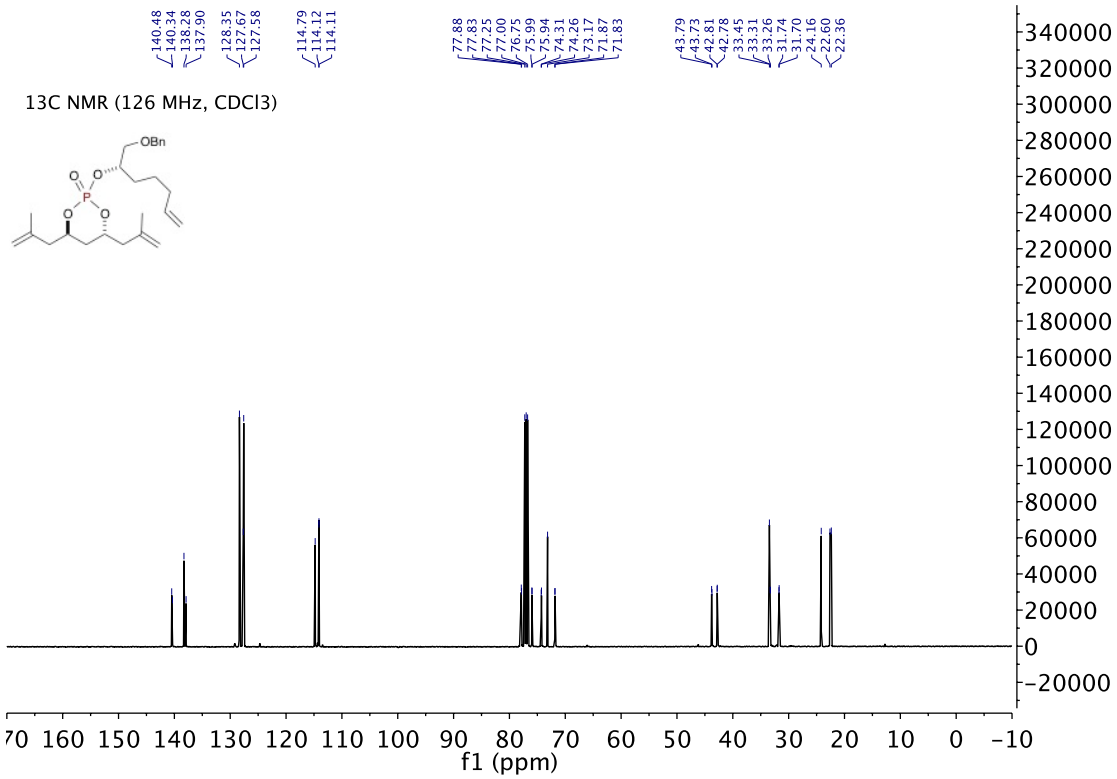

HSQC (CDCl3)
f2 (ppm)
f1 (ppm)

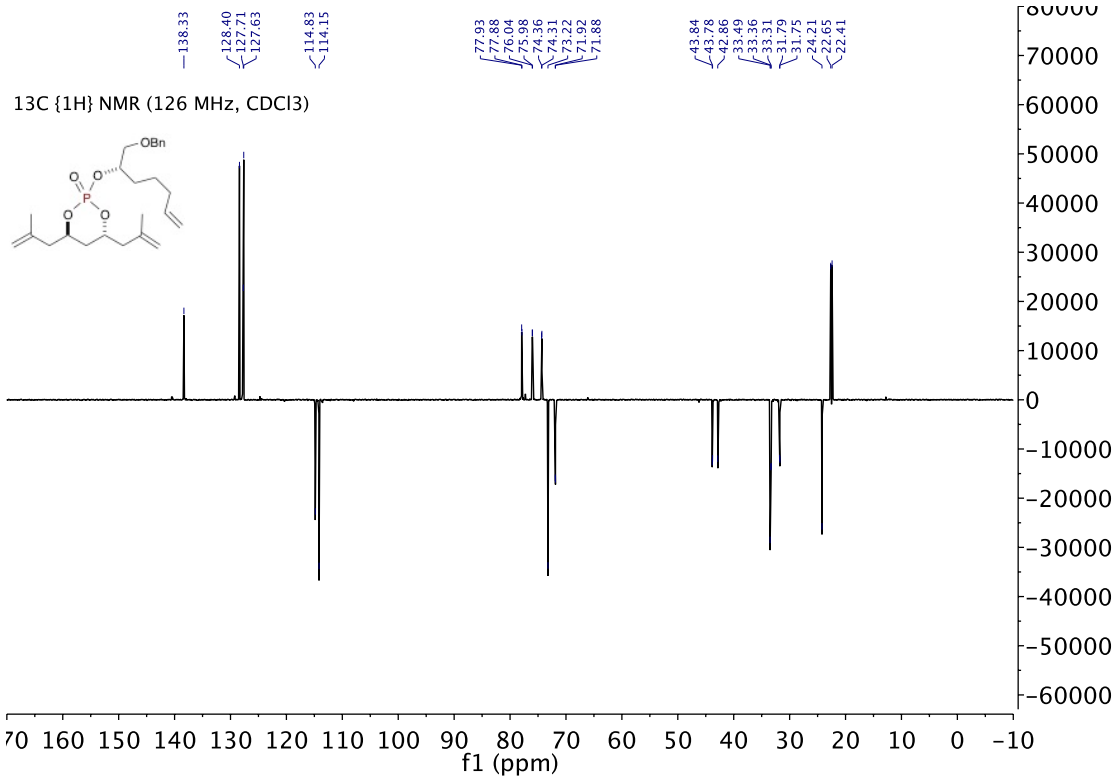

HMBC (CDCl3)
f2 (ppm)
f1 (ppm)

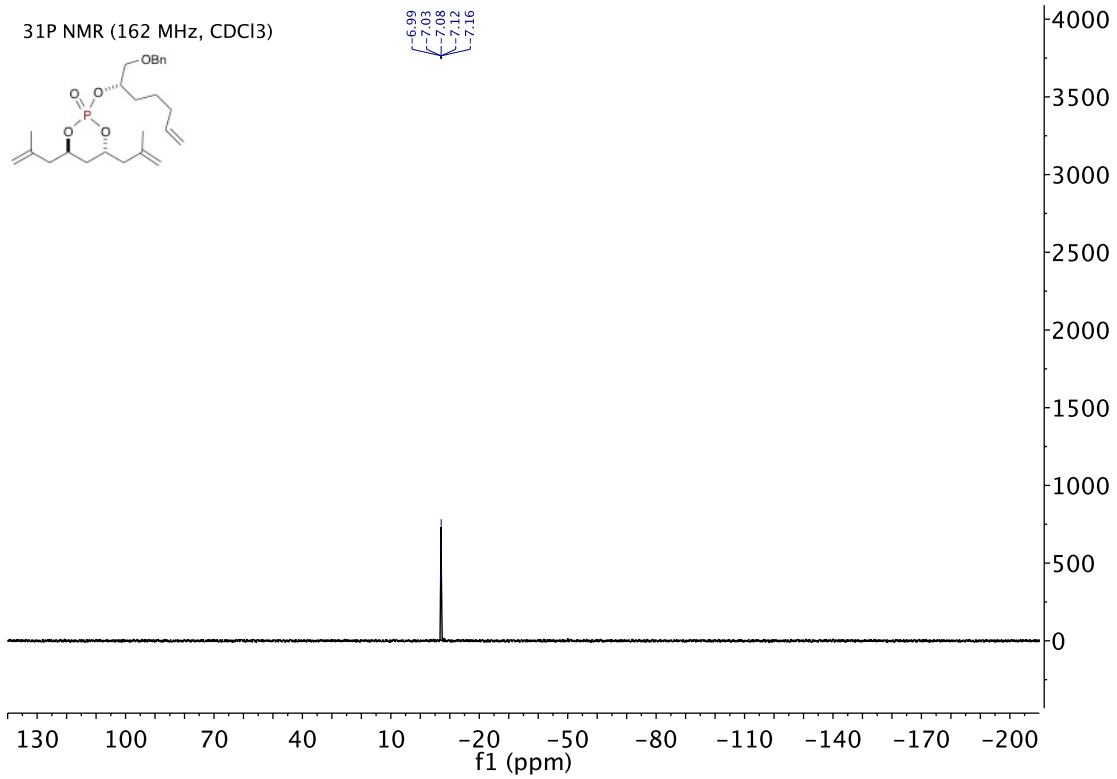

NOESY (CDCl3)
{5.19,1.79}
{3.31,2.60}
{2.60,3.31}
{1.79,5.18}
nOE
Correlation
nOE
Correlation
C7 (5.18) to CH3 (1.79)
C9 (3.31) to C6 (2.60)
f2 (ppm)
f1 (ppm)

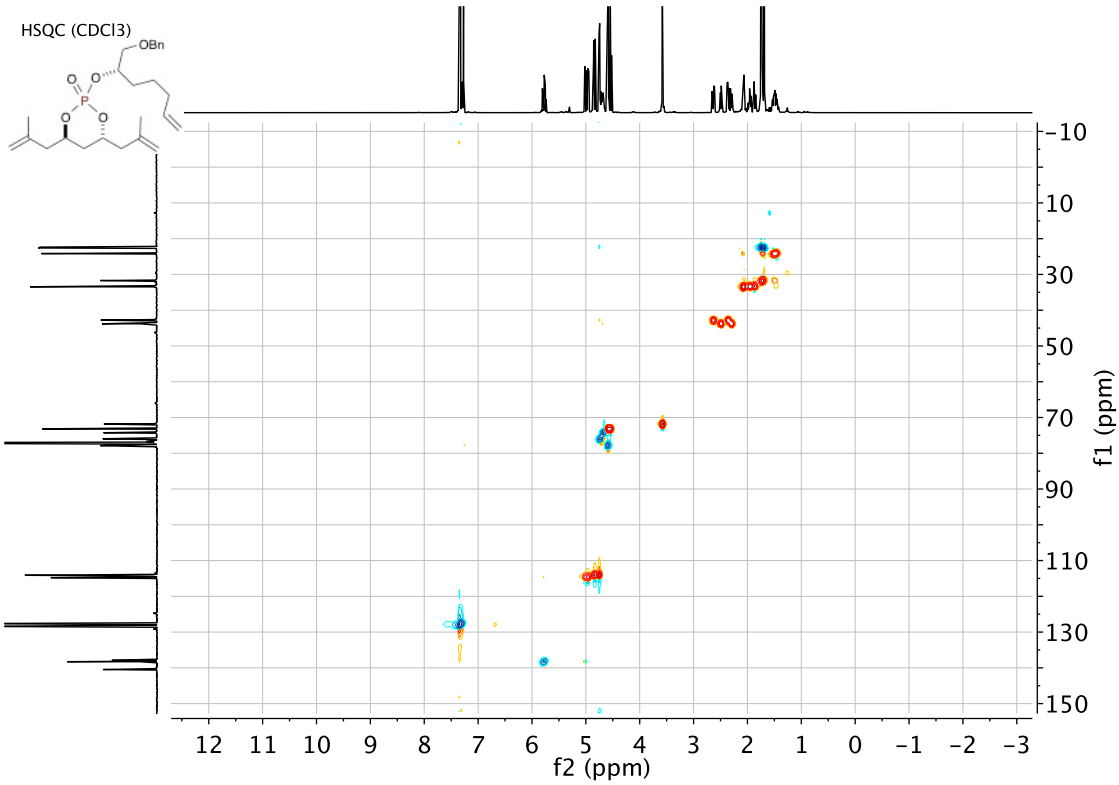
**(4*R*,6*R*)-2-(((*S*)-1-(benzyloxy)hept-6-en-2-yl)oxy)-4,6-bis(2-methylallyl)-1,3,2-dioxaphosphinane 2-oxide (2.16.3)**

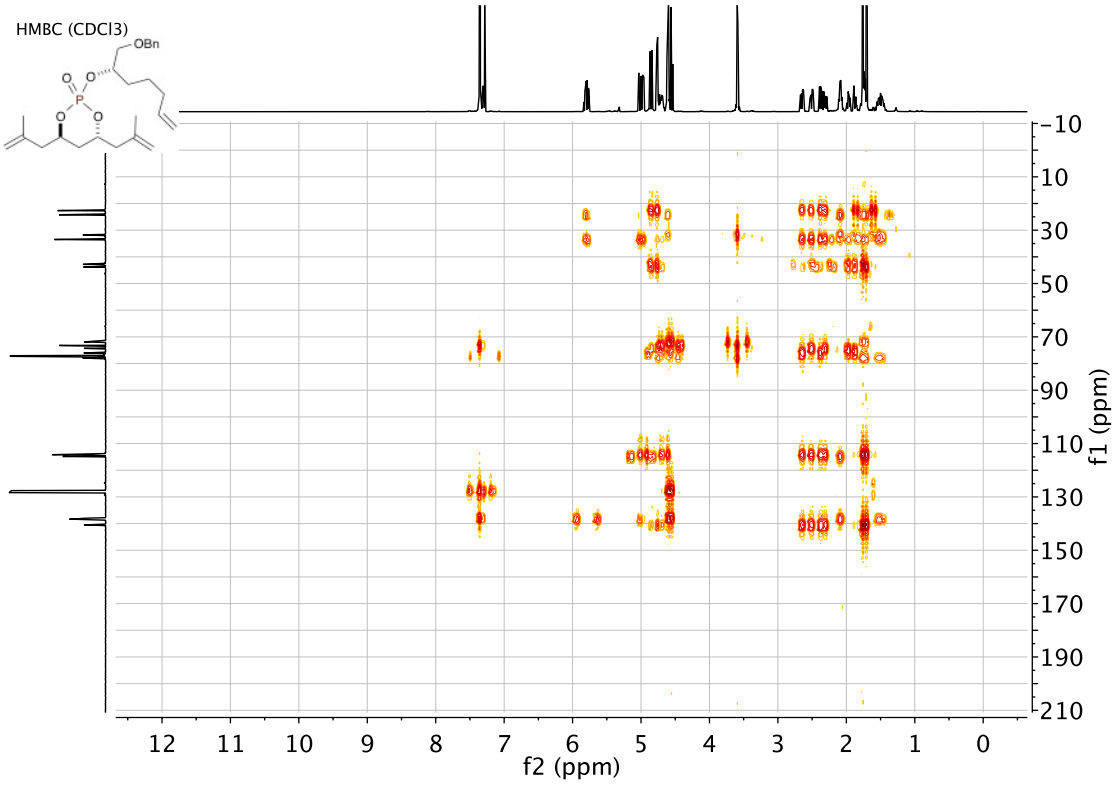



13C NMR (126 MHz, CDCl3)
OBn
140.48
140.34
138.28
137.90
128.35
127.67
127.58
114.79
114.12
114.11
77.88
77.83
77.25
77.00
76.75
75.99
75.94
74.31
74.26
73.17
71.87
71.83
43.79
43.73
42.81
42.78
33.45
33.31
33.26
31.74
31.70
24.16
22.60
22.36
340000
320000
300000
280000
260000
240000
220000
200000
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
-20000
70 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

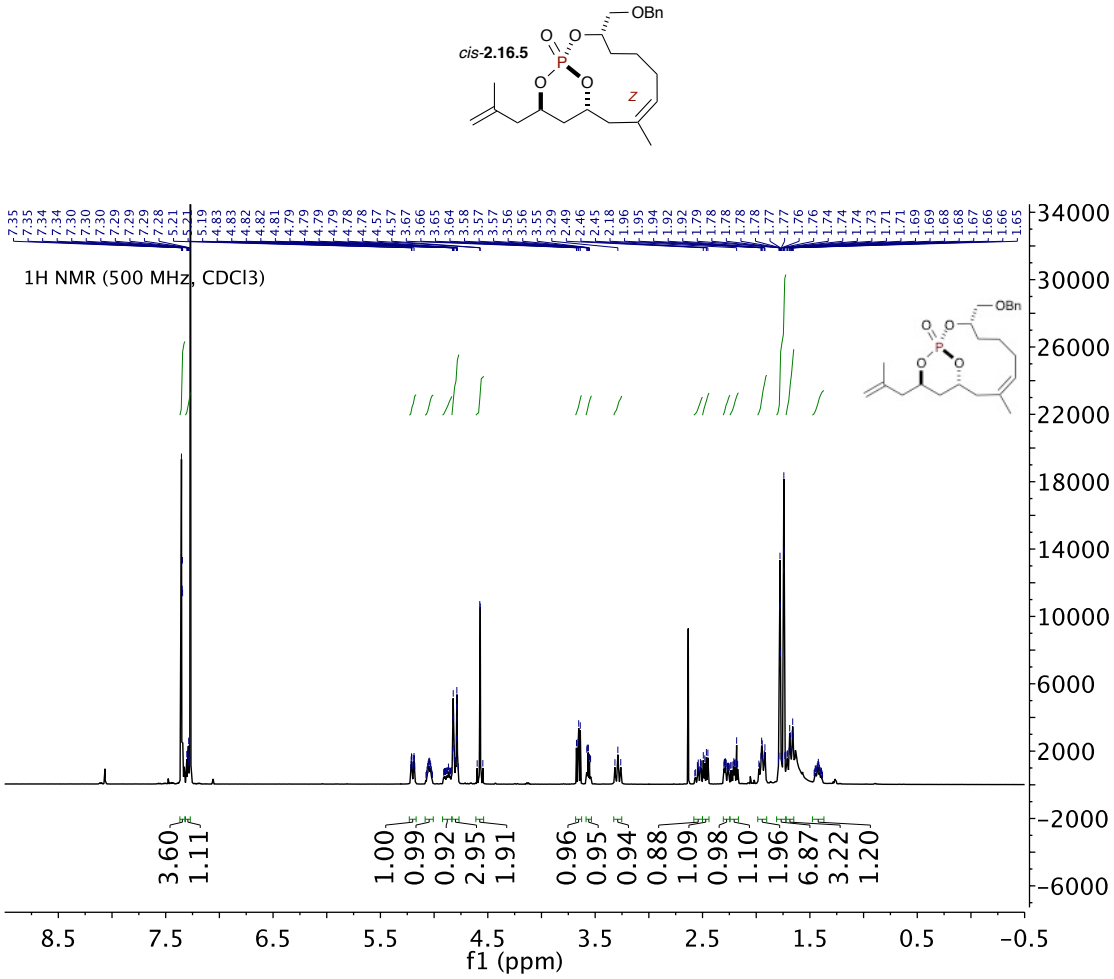

13C {1H} NMR (126 MHz, CDCl3)
OBn
138.33
128.40
127.71
127.63
114.83
114.15
77.93
77.88
76.04
75.98
74.36
74.31
73.22
71.92
71.88
43.84
43.78
42.86
33.49
33.36
33.31
31.79
31.75
24.21
22.65
22.41
70000
60000
50000
40000
30000
20000
10000
0
-10000
-20000
-30000
-40000
-50000
-60000
70 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

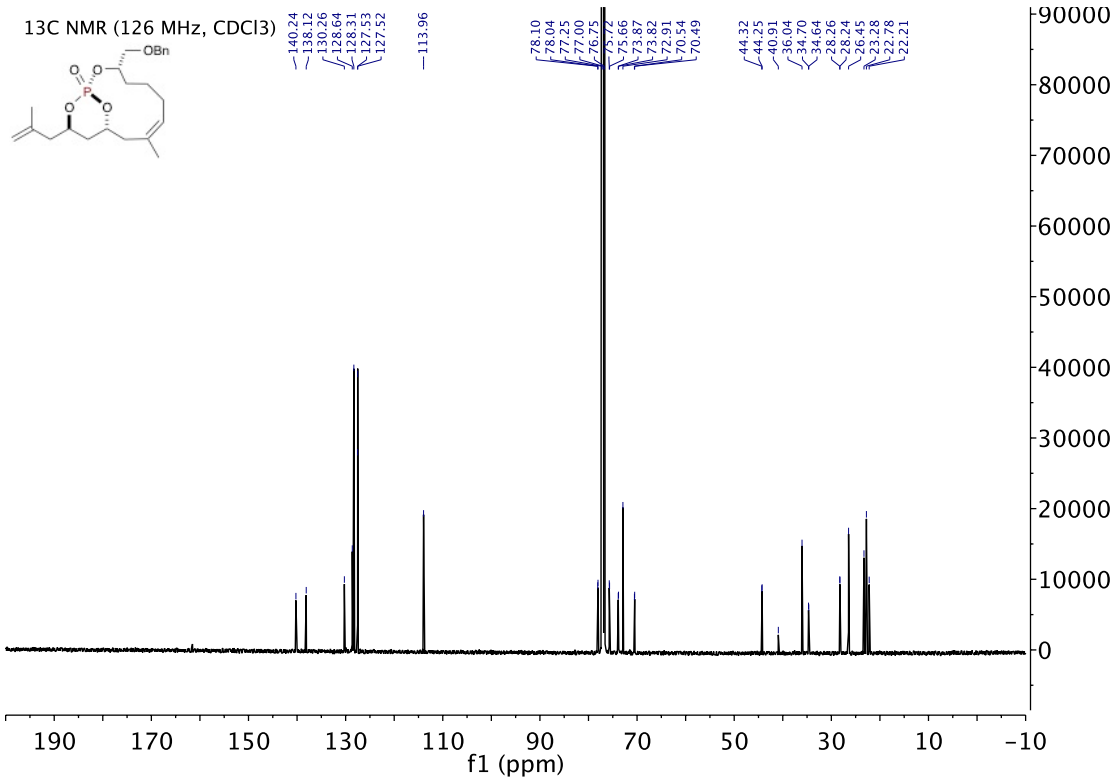

31P NMR (162 MHz, CDCl3)
OBn
6.99
7.03
7.08
7.12
7.16
4000
3500
3000
2500
2000
1500
1000
500
0
130
100
70
40
10
-20
-50
-80
-110
-140
-170
-200
f1 (ppm)

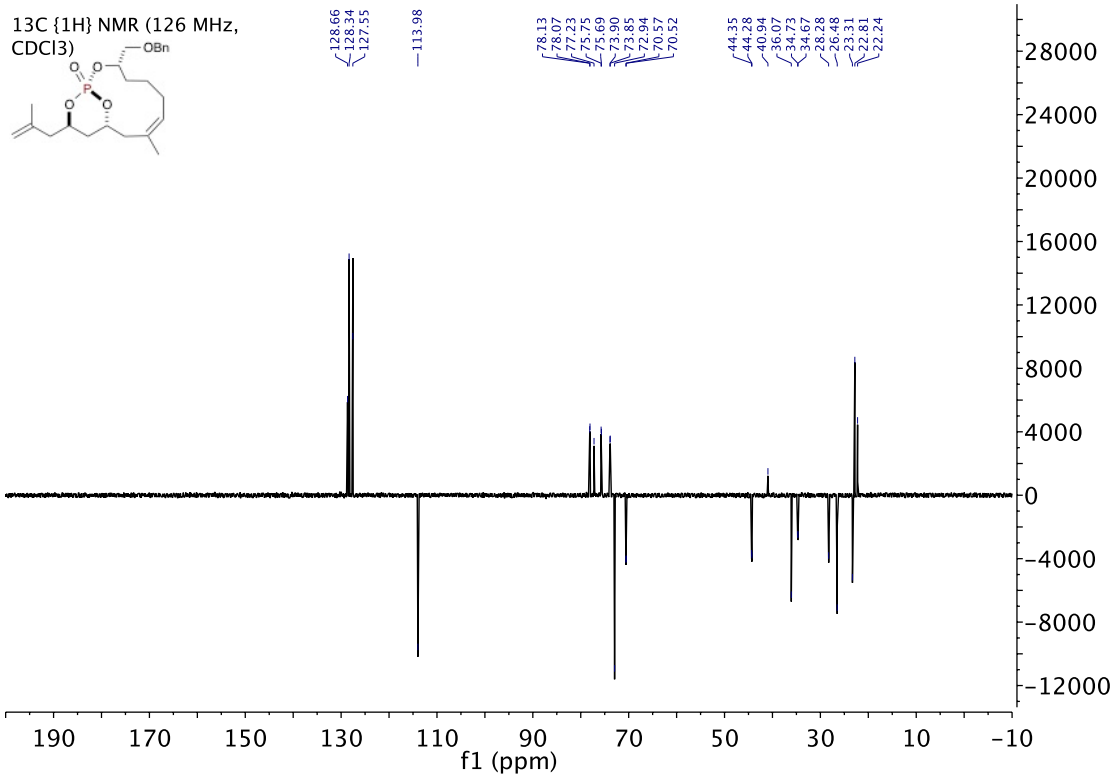

HSQC (CDCl3)
OBn
-10
10
30
50
70
90
110
130
150
f1 (ppm)
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
f2 (ppm)

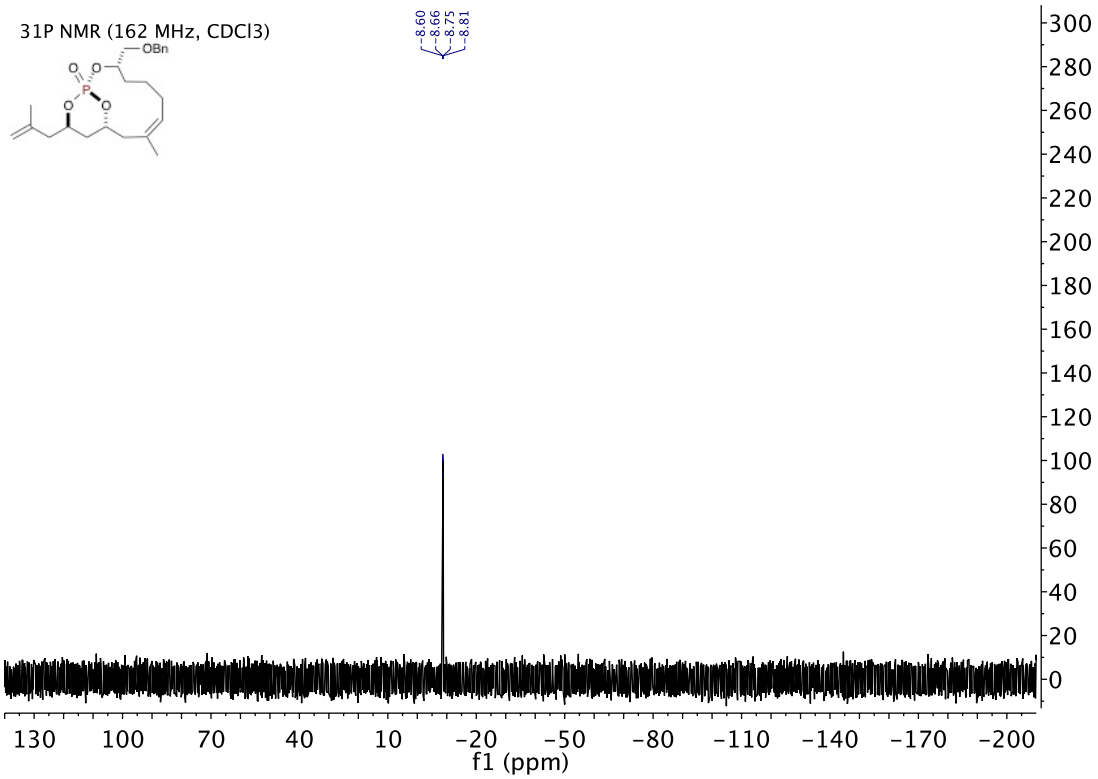

HMBC (CDCl3)
OBn
f2 (ppm)
f1 (ppm)

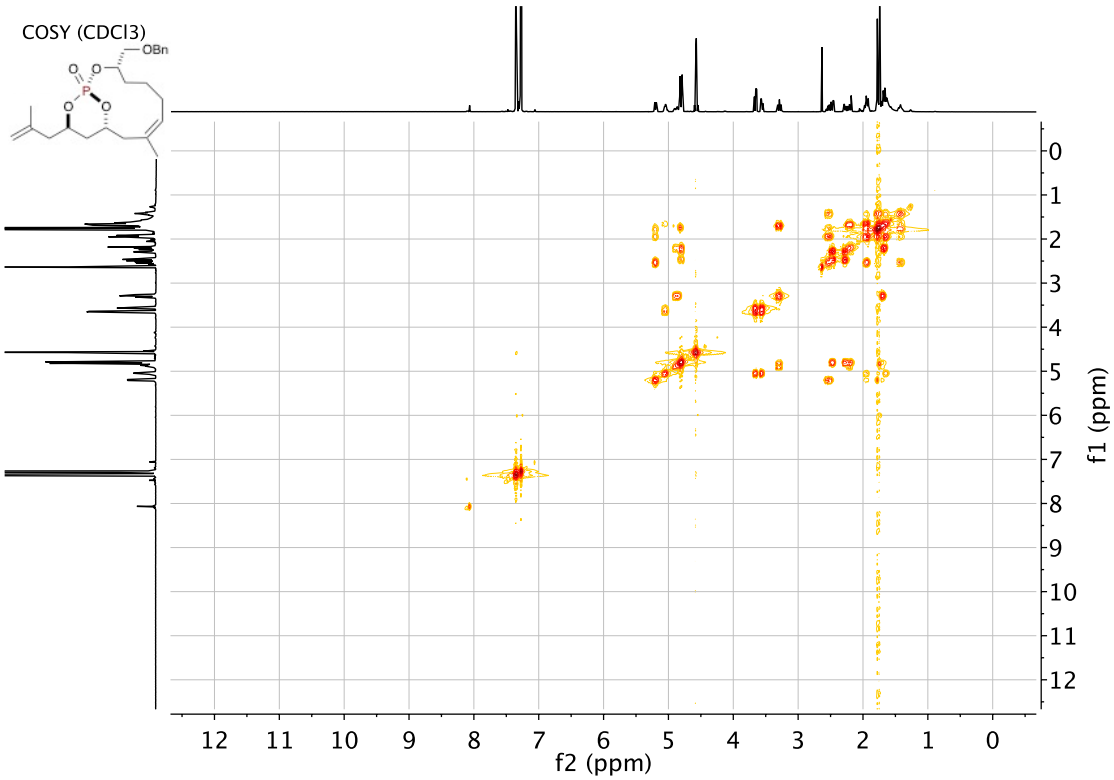
**(1*S*,3*S*,10*R*,12*R*,*Z*)-3-((benzyloxy)methyl)-8-methyl-12-(2-methylallyl)-2,13,14-trioxa-1-phosphabicyclo[8.3.1]tetradec-7-ene 1-oxide (*cis*-2.16.5)**

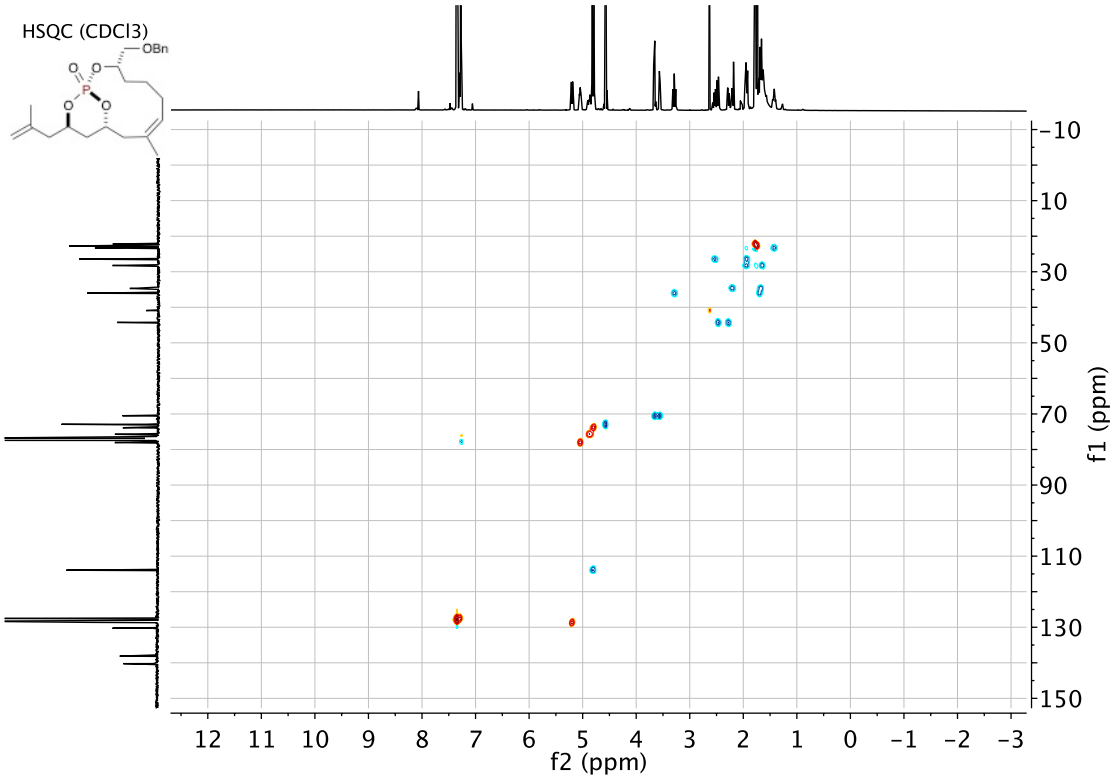


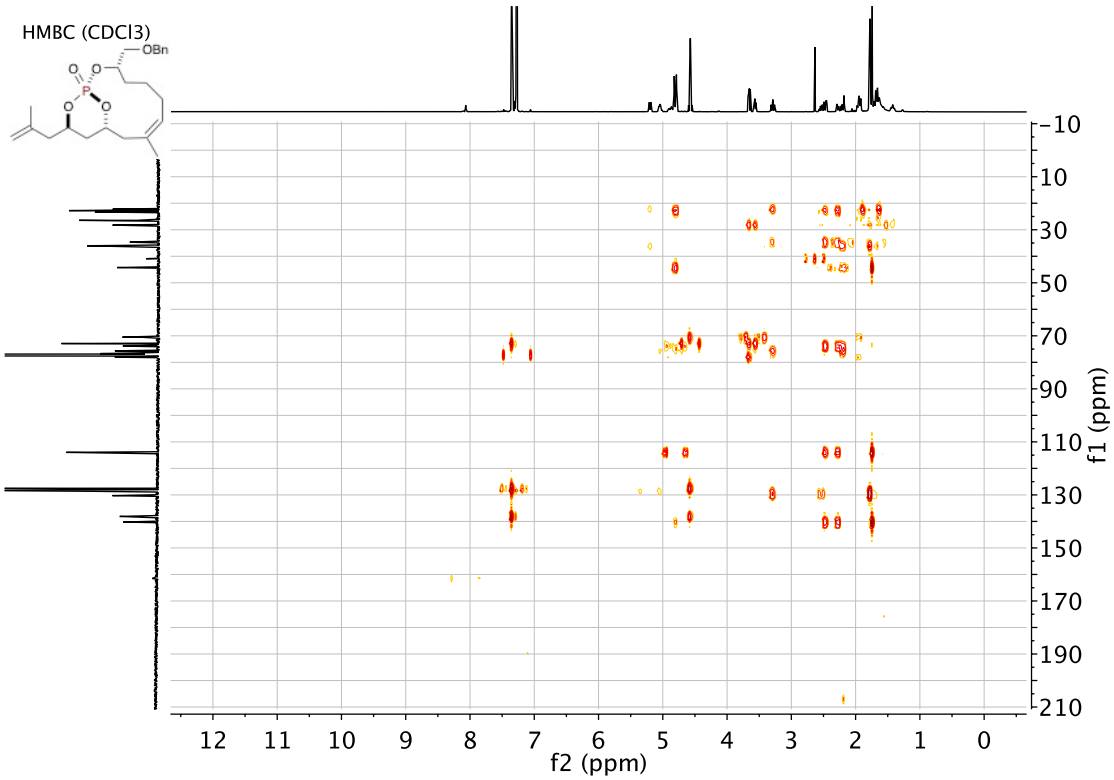

13C NMR (126 MHz, CDCl3)
OBn
140.24
138.12
130.26
128.64
128.31
127.53
127.52
113.96
78.10
78.04
77.25
77.00
76.75
75.72
75.66
73.87
73.82
72.91
70.54
70.49
44.32
44.25
40.91
36.04
34.70
34.64
28.26
28.24
26.45
23.28
22.78
22.21
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

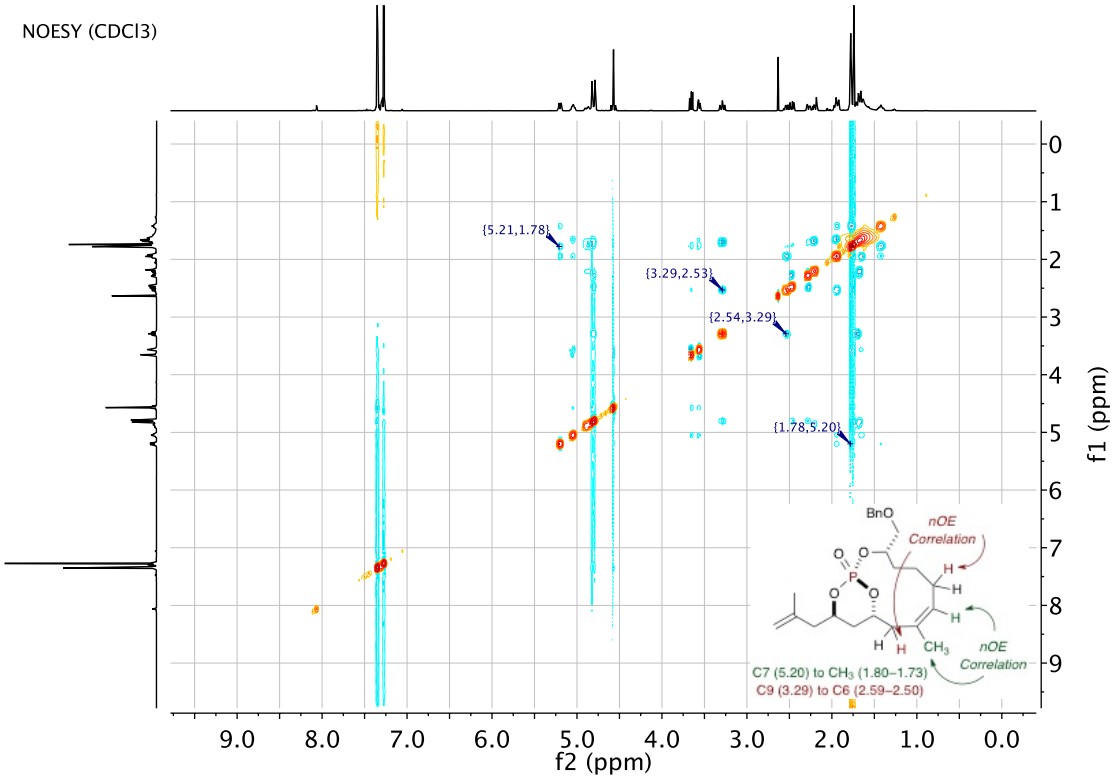

13C {1H} NMR (126 MHz, CDCl3)
OBn
128.66
128.34
127.55
113.98
78.13
78.07
77.23
75.75
75.69
73.90
73.85
72.94
70.57
70.52
44.35
44.28
40.94
36.07
34.73
34.67
28.28
26.48
23.31
22.81
22.24
28000
24000
20000
16000
12000
8000
4000
0
-4000
-8000
-12000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)


31P NMR (162 MHz, CDCl3)
OBn
8.60
8.66
8.75
8.81
f1 (ppm)

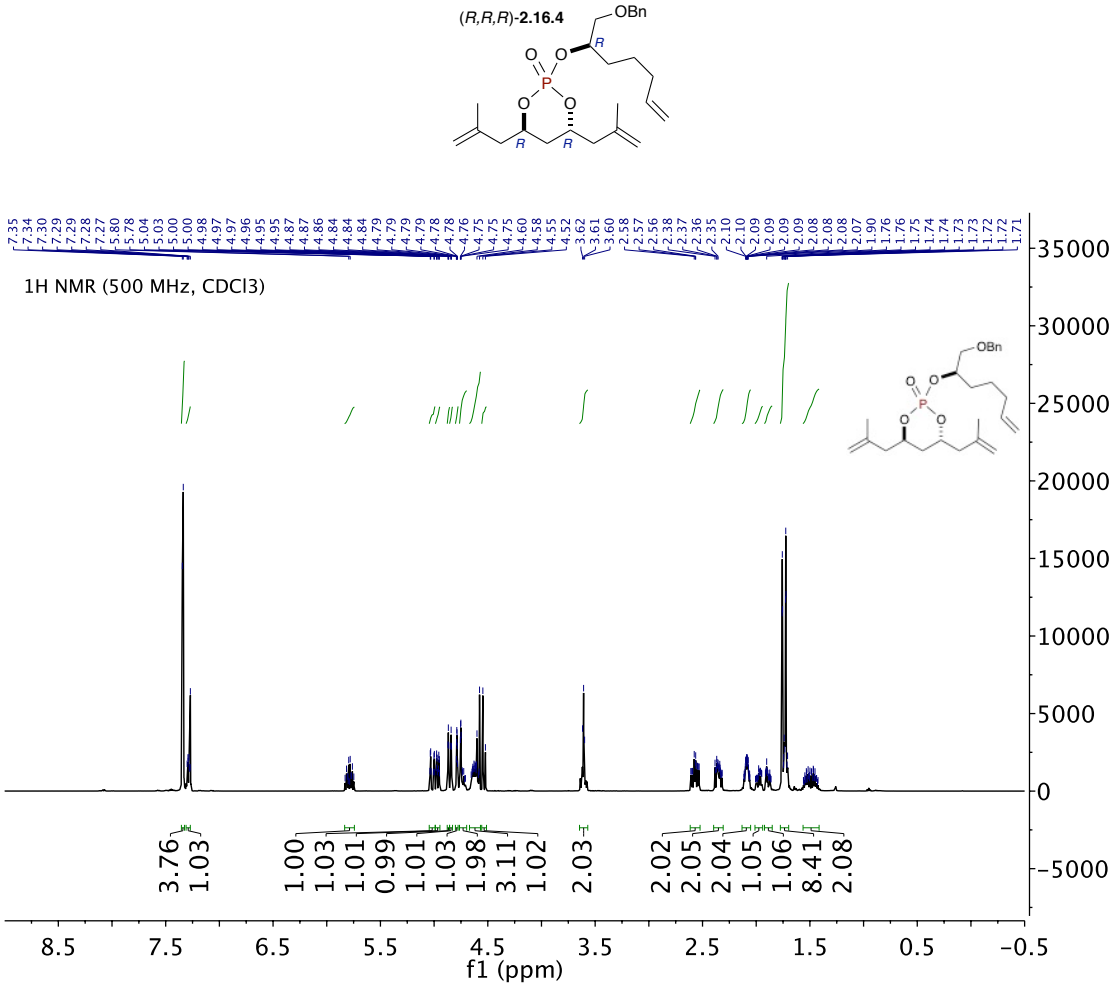

COSY (CDCl3)
OBn
f2 (ppm)
f1 (ppm)

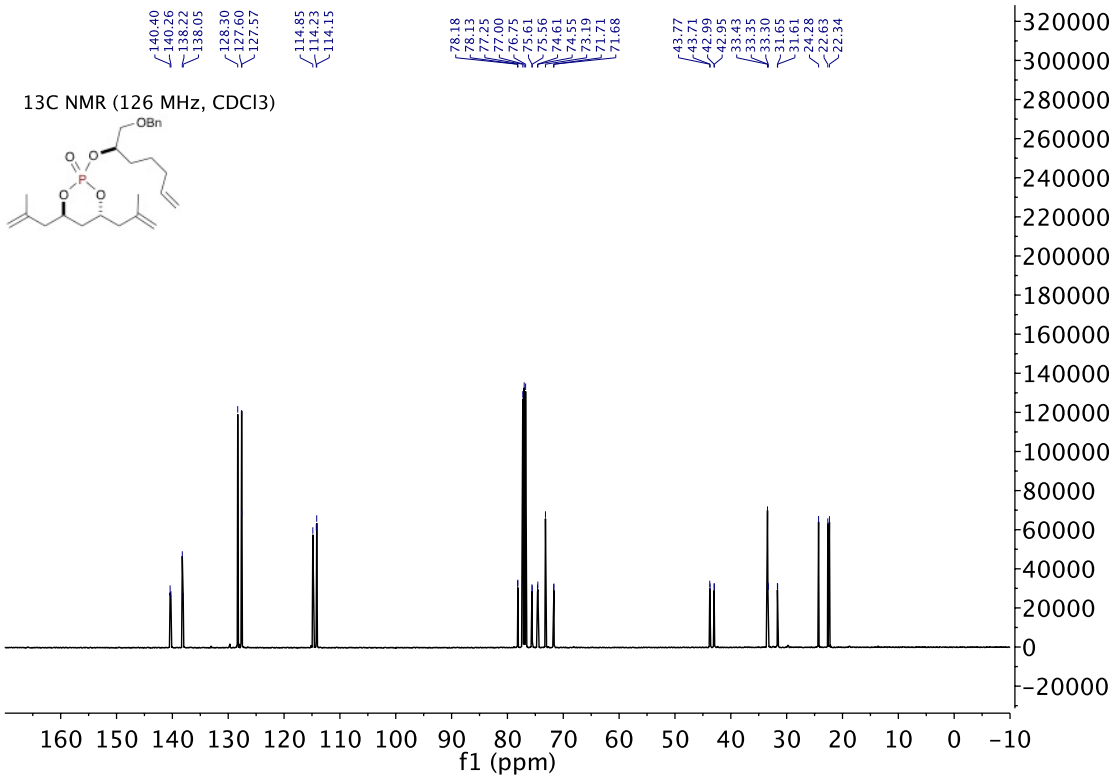

HSQC (CDCl3)
OBn
f2 (ppm)
f1 (ppm)

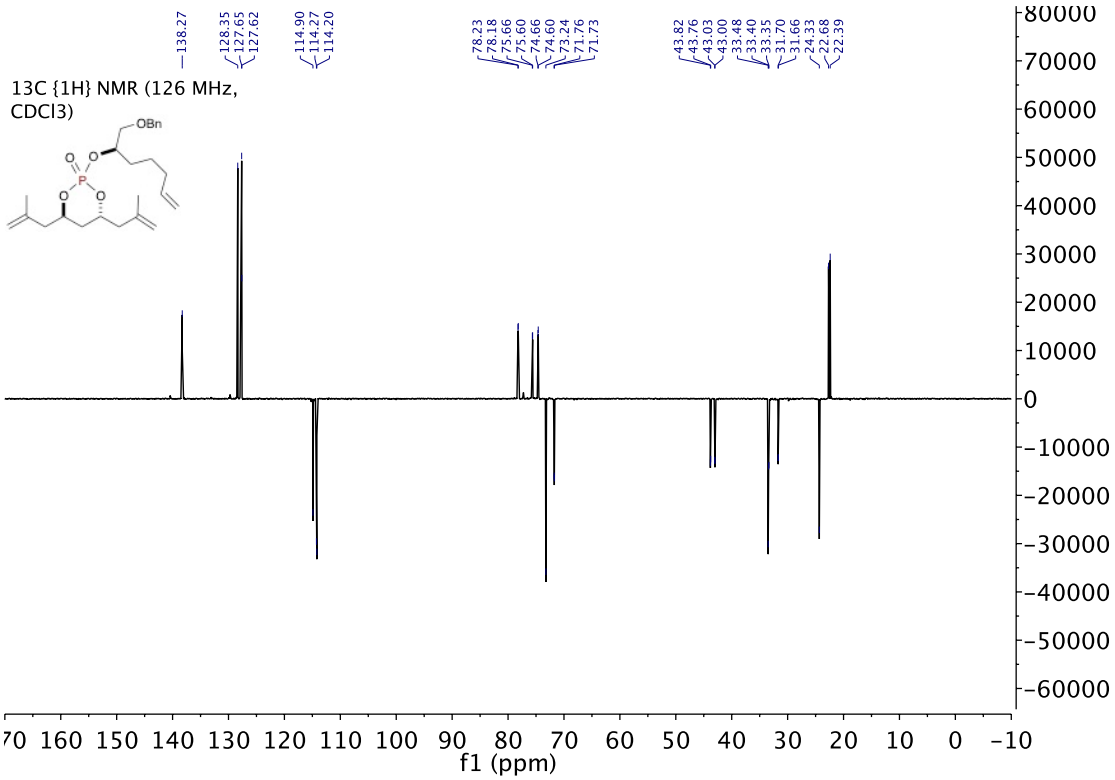

HMBC (CDCl3)
OBn
f2 (ppm)
f1 (ppm)

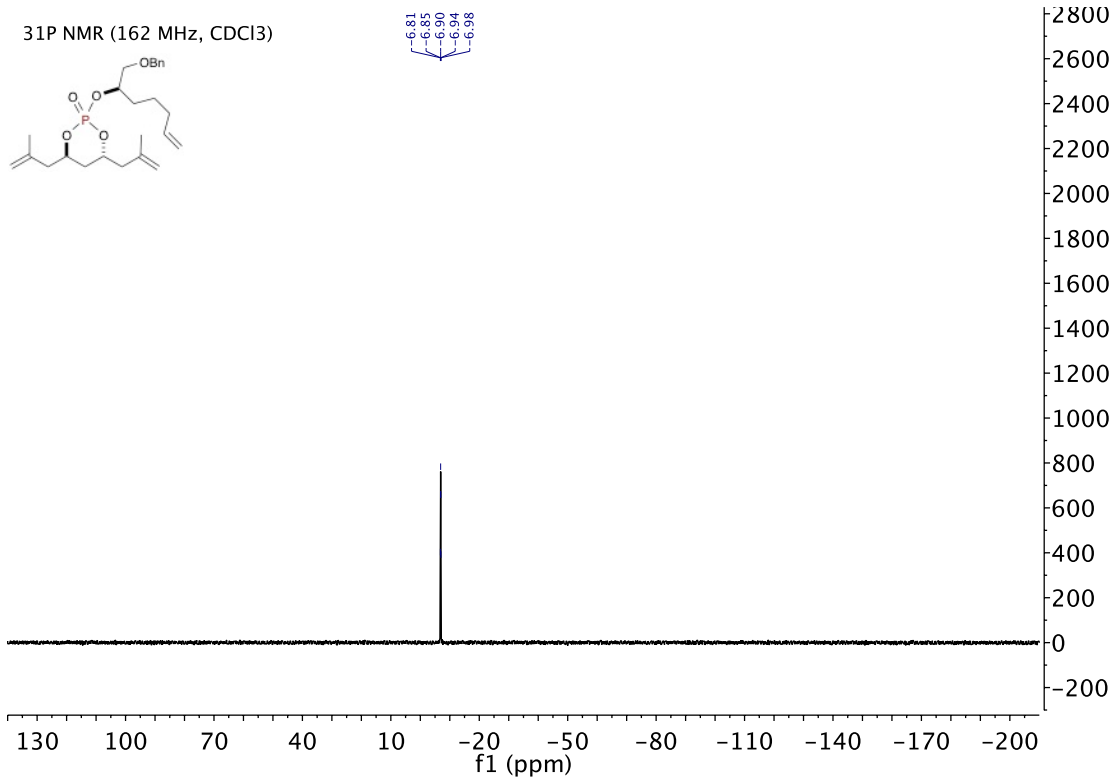

NOESY (CDCl3)
{5.21,1.78}
{3.29,2.53}
{2.54,3.29}
{1.78,5.20}
BnO
nOE
Correlation
H
H
H
H
H
CH3
nOE
Correlation
C7 (5.20) to CH3 (1.80–1.73)
C9 (3.29) to C6 (2.59–2.50)
f2 (ppm)
f1 (ppm)

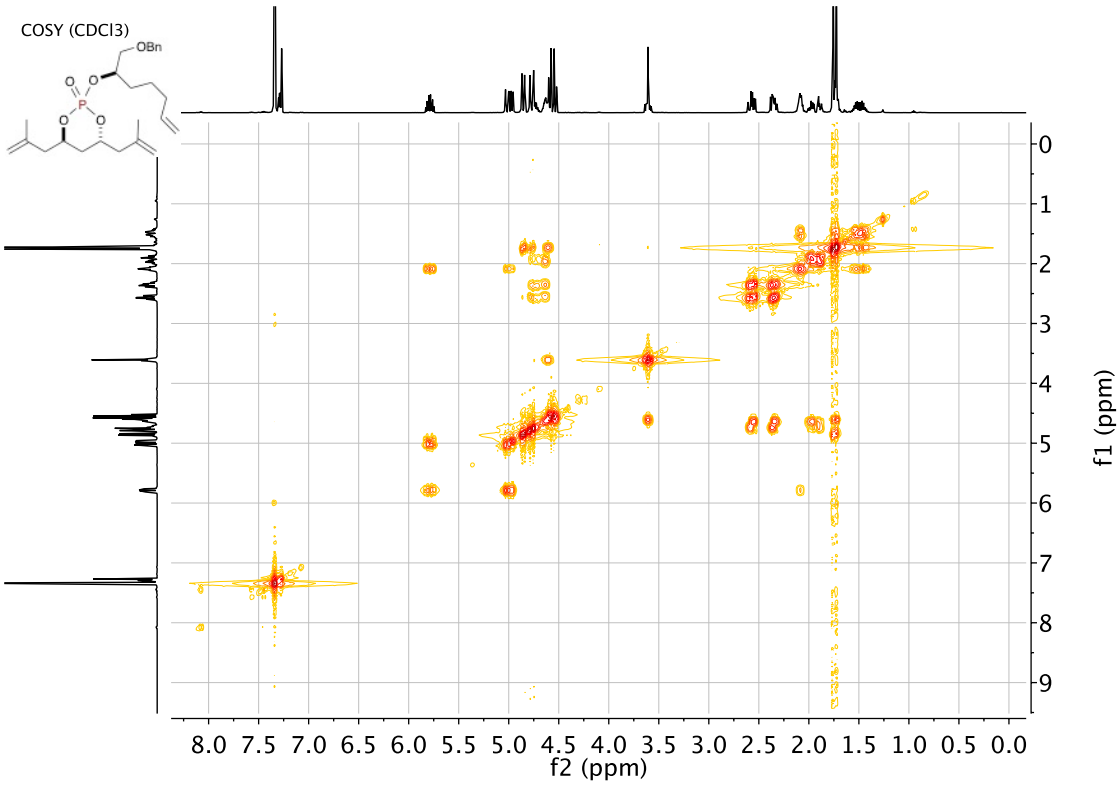
**(4*R*,6*R*)-2-(((*R*)-1-(benzyloxy)hept-6-en-2-yl)oxy)-4,6-bis(2-methylallyl)-1,3,2-dioxaphosphinane 2-oxide (2.16.4)**

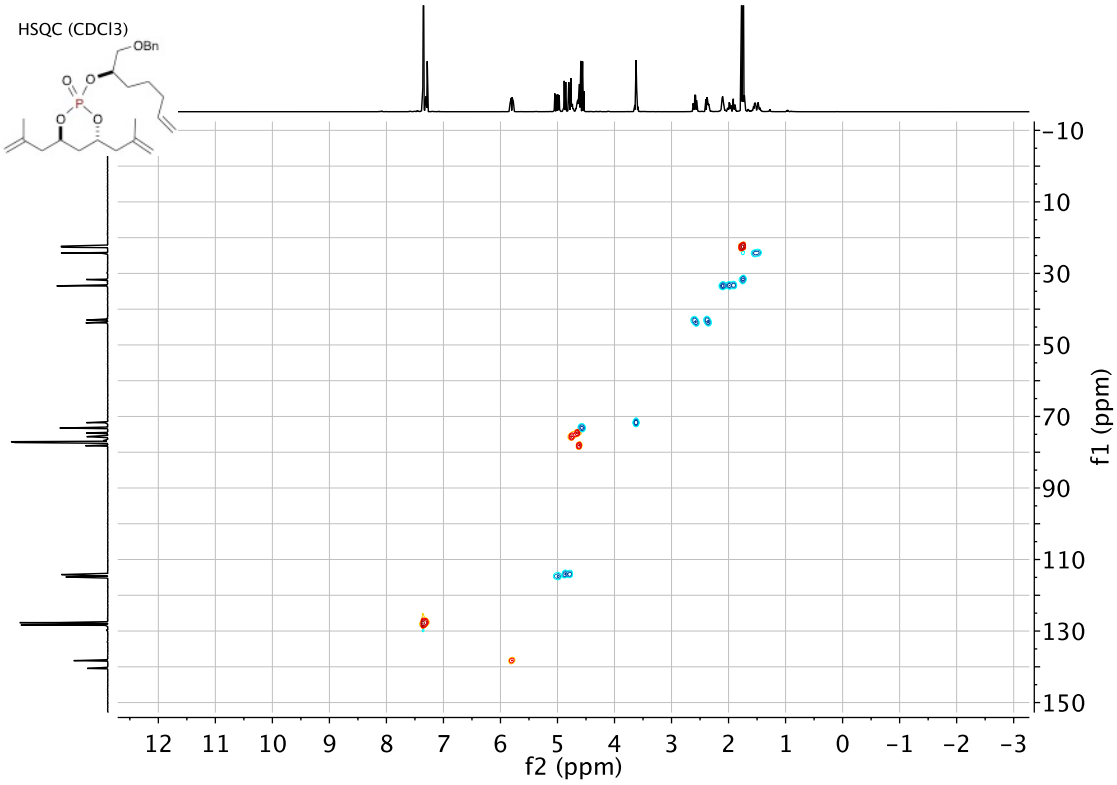



13C NMR (126 MHz, CDCl3)
OBn
140.40
140.26
138.22
138.05
128.30
127.60
127.57
114.85
114.23
114.15
78.18
78.13
77.25
77.00
76.75
75.61
75.56
74.61
74.55
73.19
71.71
71.68
43.77
43.71
42.99
42.95
33.43
33.35
33.30
31.65
31.61
24.28
22.63
22.34
f1 (ppm)

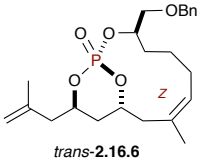

13C {1H} NMR (126 MHz, CDCl3)
OBn
138.27
128.35
127.65
127.62
114.90
114.27
114.20
78.23
78.18
75.66
75.60
74.66
74.60
73.24
71.76
71.73
43.82
43.76
43.03
43.00
33.48
33.40
33.35
31.70
31.66
24.33
22.68
22.39
f1 (ppm)


31P NMR (162 MHz, CDCl3)
OBn
6.81
6.85
6.90
6.94
6.98
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
130
100
70
40
10
-20
-50
-80
-110
-140
-170
-200
f1 (ppm)

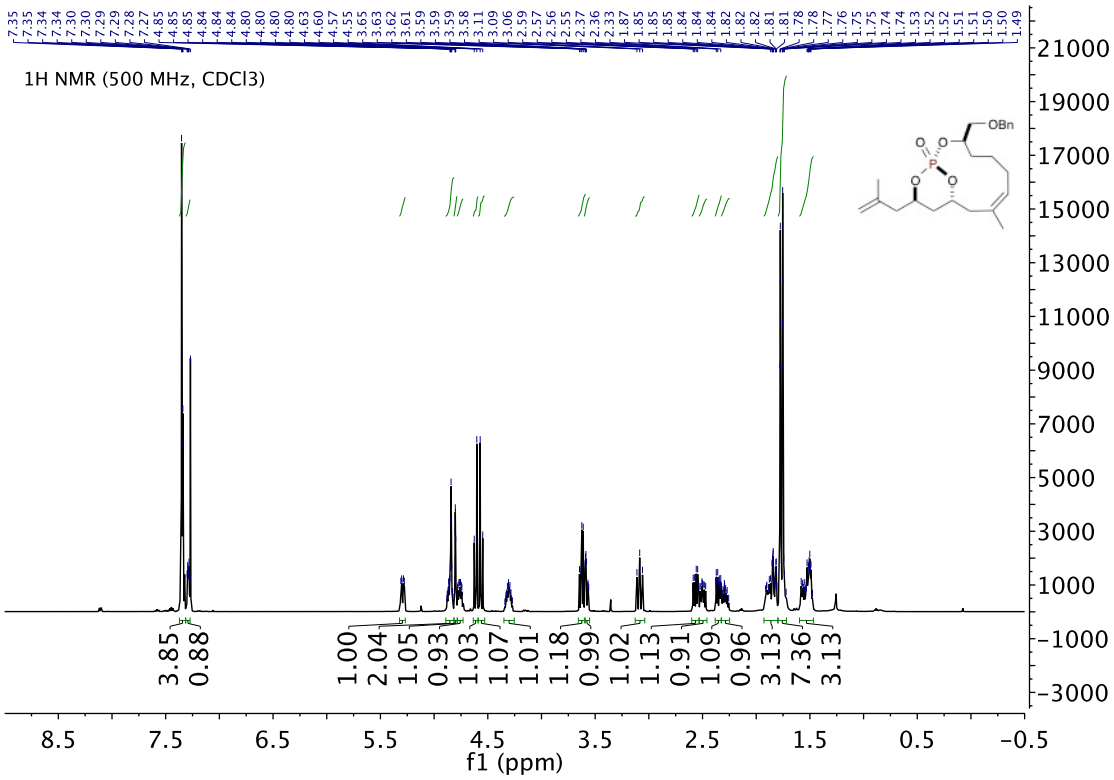

COSY (CDCl3)
OBn
0
1
2
3
4
5
6
7
8
9
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f2 (ppm)

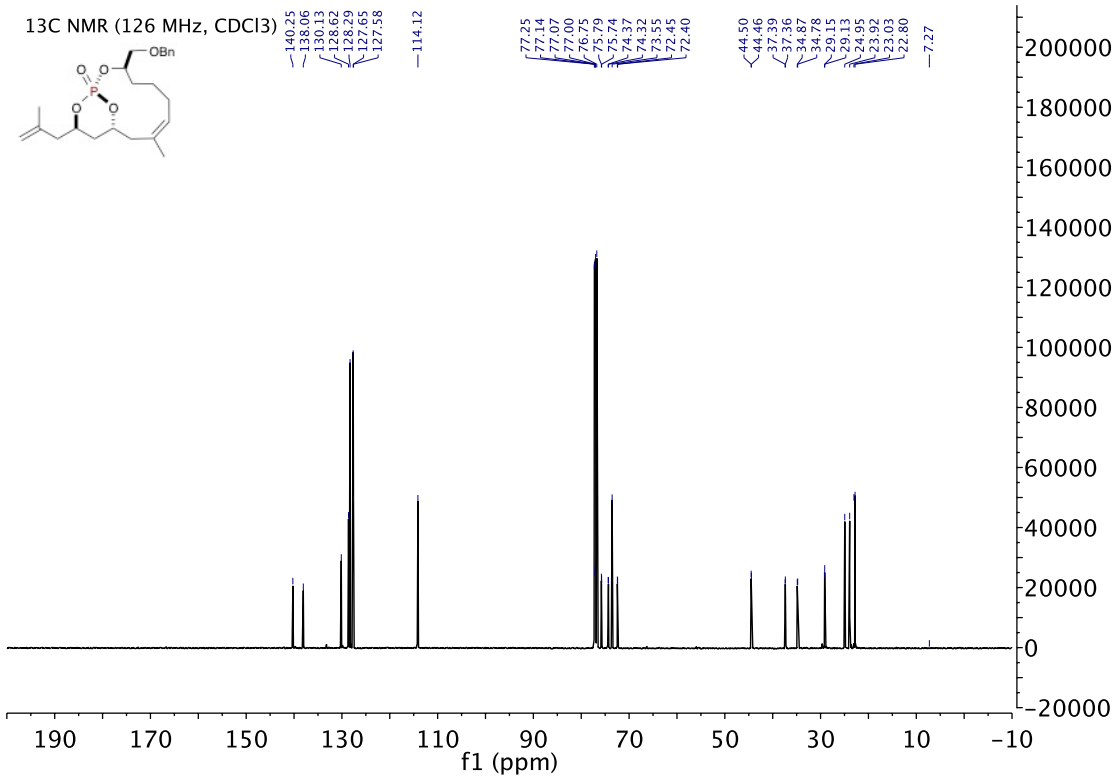

HSQC (CDCl3)
OBn
f2 (ppm)
f1 (ppm)

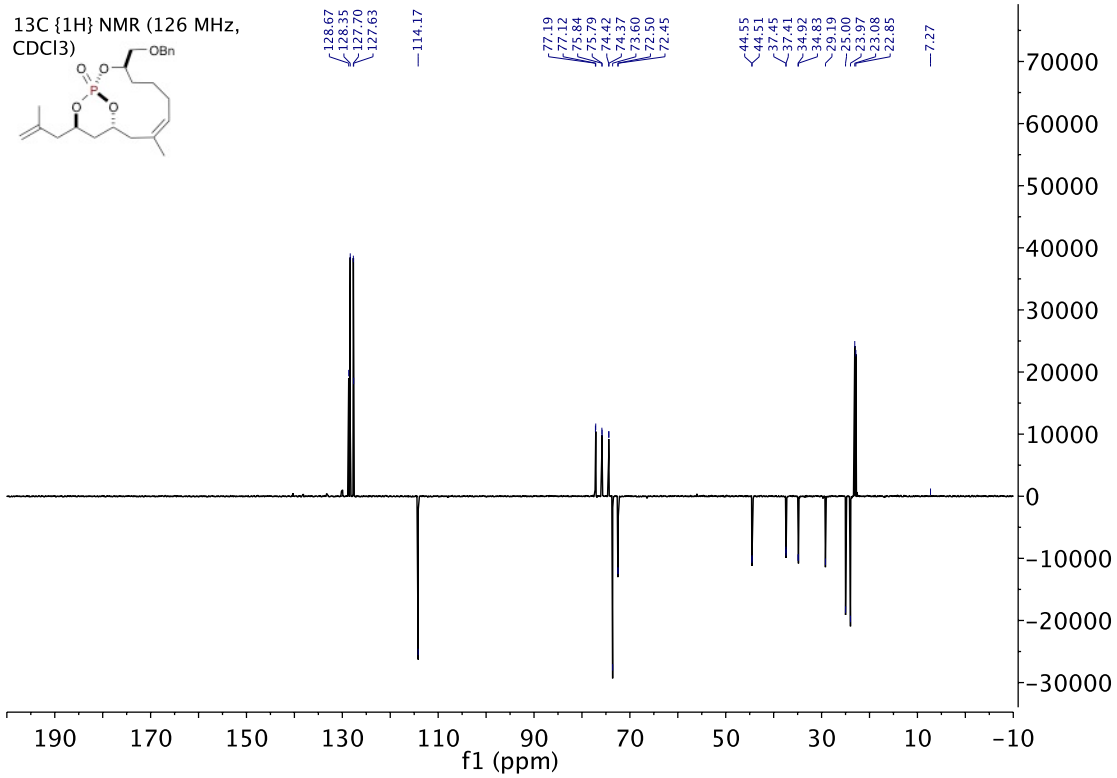
**(1*S*,3*R*,10*R*,12*R*,*Z*)-3-((benzyloxy)methyl)-8-methyl-12-(2-methylallyl)-2,13,14-trioxa-1-phosphabicyclo[8.3.1]tetradec-7-ene 1-oxide (*trans*-2.16.6)**

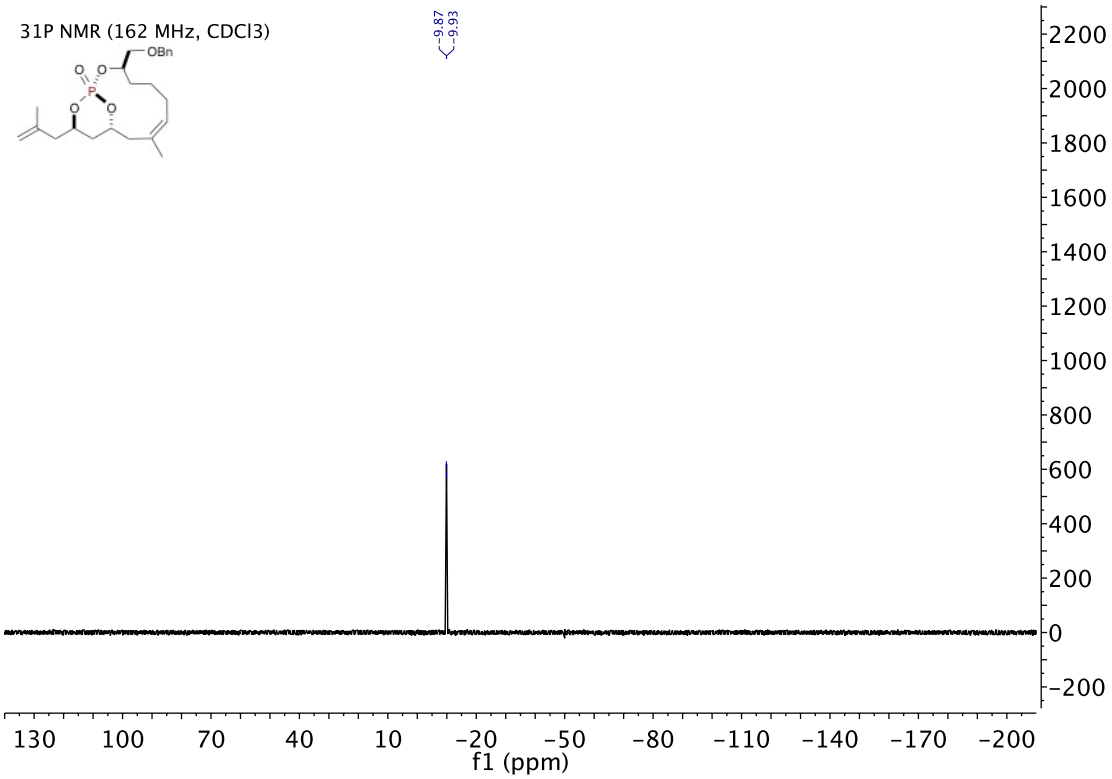


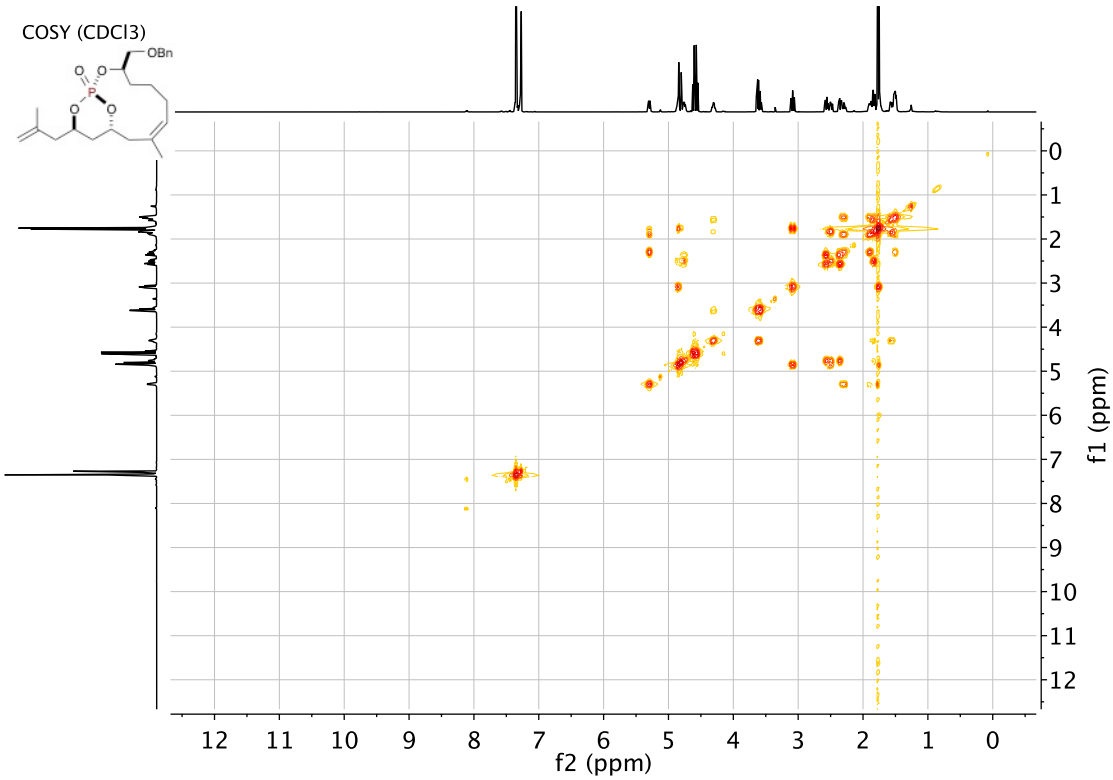

*trans*-**2.16.6**

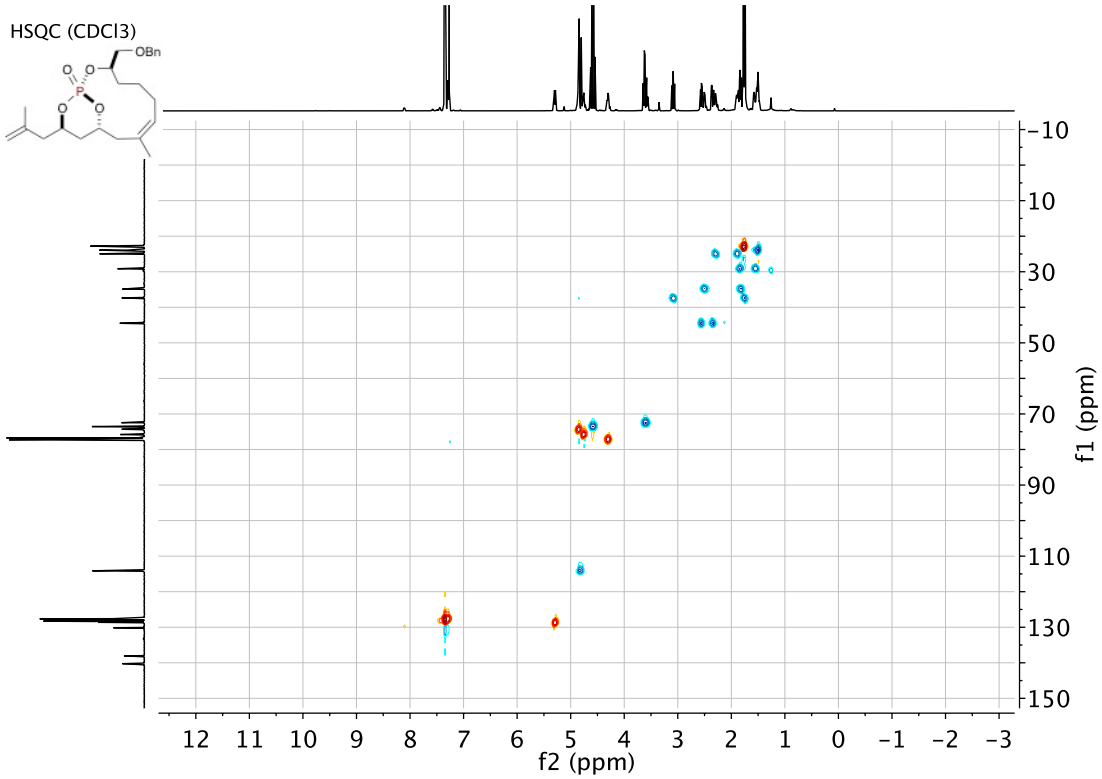


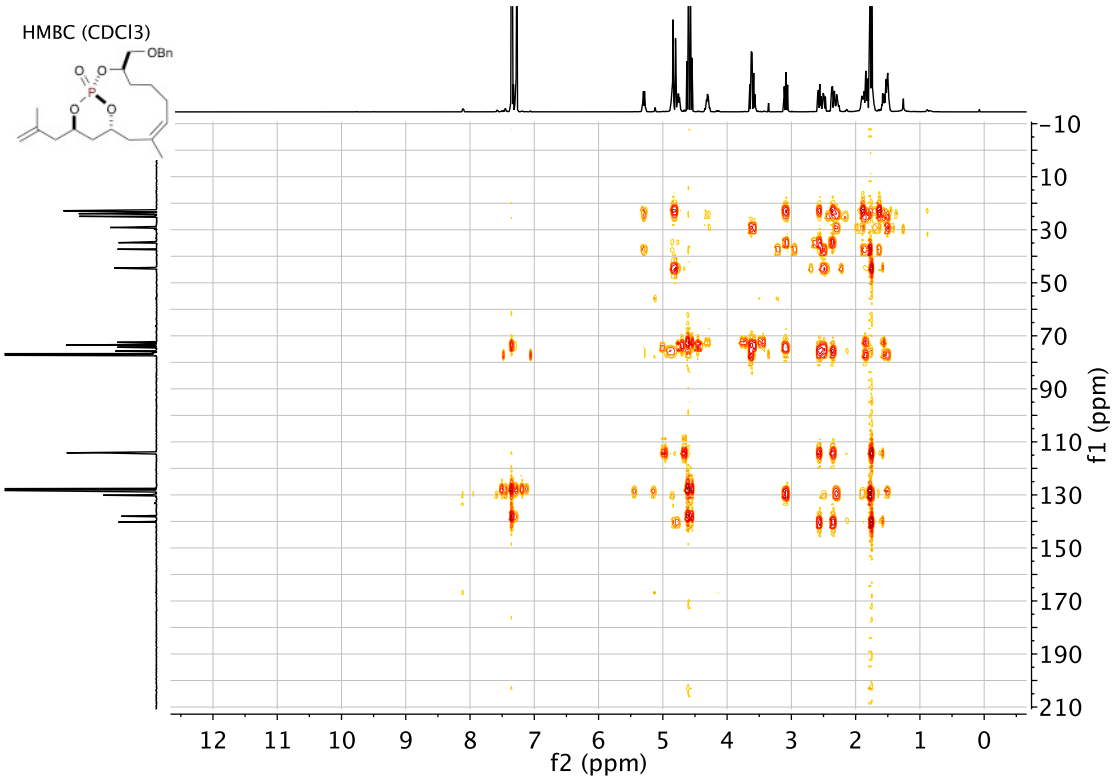

13C NMR (126 MHz, CDCl3)
OBn
140.25
138.06
130.13
128.62
128.29
127.65
127.58
114.12
77.25
77.14
77.07
77.00
76.75
75.79
75.74
74.37
74.32
73.55
72.45
72.40
44.50
44.46
37.39
37.36
34.87
34.78
29.15
29.13
24.95
23.92
23.03
22.80
7.27
200000
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
-20000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

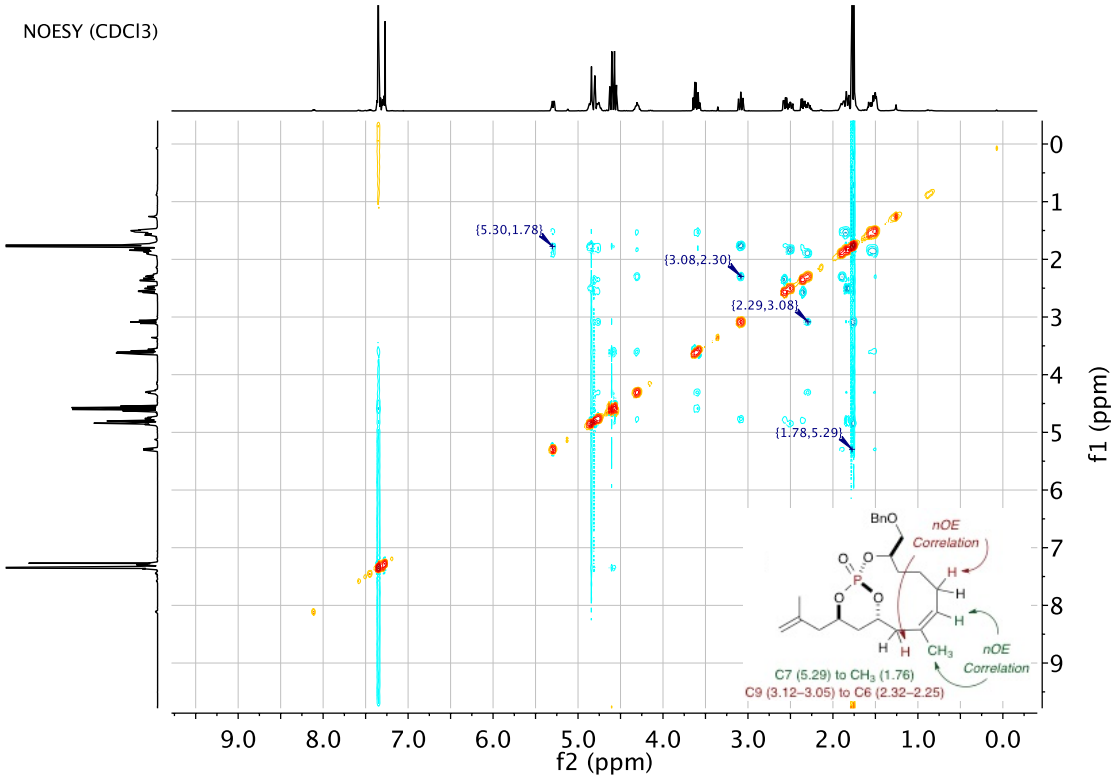

13C {1H} NMR (126 MHz, CDCl3)
OBn
128.67
128.35
127.70
127.63
114.17
77.19
77.12
75.84
75.79
74.42
74.37
73.60
72.50
72.45
44.55
44.51
37.45
37.41
34.92
34.83
29.19
25.00
23.97
23.08
22.85
7.27
70000
60000
50000
40000
30000
20000
10000
0
-10000
-20000
-30000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)


31P NMR (162 MHz, CDCl3)
OBn
-9.87
-9.93
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
130
100
70
40
10
-20
-50
-80
-110
-140
-170
-200
f1 (ppm)


COSY (CDCl3)
OBn
0
1
2
3
4
5
6
7
8
9
10
11
12
f1 (ppm)
12
11
10
9
8
7
6
5
4
3
2
1
0
f2 (ppm)


HSQC (CDCl3)
OBn
f2 (ppm)
f1 (ppm)


HMBC (CDCl3)
OBn
f2 (ppm)
f1 (ppm)


NOESY (CDCl3)
{5.30,1.78}
{3.08,2.30}
{2.29,3.08}
{1.78,5.29}
BnO
nOE
Correlation
H
H
H
H
H
CH3
nOE
Correlation
C7 (5.29) to CH3 (1.76)
C9 (3.12–3.05) to C6 (2.32–2.25)
f2 (ppm)
f1 (ppm)

## 5.2 Supporting Information for Chapter 3

*Bicyclo[4.3.1]Phosphite Boranes: Tunable P-Tether Systems for the Synthesis of 1,3-Skipped Polyol Stereotetrads*

# *Table of Contents*

## Chapter 5, Section 2: Supporting Information for Chapter 2

*Bicyclo[4.3.1]Phosphite Boranes: Tunable P-Tether Systems for the Synthesis of 1,3-Skipped Polyol Stereotetrads*

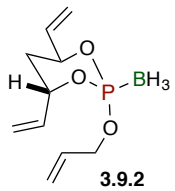
### 5.2.1 General Methods

All reactions were carried out in oven- or flame-dried glassware under argon atmosphere using standard gas-tight syringes, cannulae, and septa. Stirring was achieved with oven-dried magnetic stir bars. $Et_2O$, THF and $CH_2Cl_2$ were purified by passage through a purification system (Solv-Tek) employing activated $Al_2O_3$ (Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520). $Et_3N$ was purified by passage over basic alumina and stored over KOH. Butyllithium was purchased from Aldrich and titrated prior to use. All olefin metathesis catalysts were acquired from Materia and used without further purification. Flash column chromatography was performed with Sorbent Technologies (30930M-25, Silica Gel 60A, 40-63 mm) and thin layer chromatography was performed on silica gel $60F_{254}$ plates (EM-5717, Merck). Deuterated solvents were purchased from Cambridge Isotope laboratories. $^{1}H$, $^{13}C$, and corresponding 2D NMR spectra were recorded in $CDCl_3$ (unless otherwise mentioned) on a Bruker DRX-500 spectrometer operating at 500 MHz, and 125 MHz, respectively and calibrated to the solvent peak. $^{31}P$ and $^{1}H$-decoupled $^{31}P$ NMR spectra were recorded on a Bruker DRX-400 spectrometer operating at 162 MHz, and $^{11}B$ NMR spectra was recorded on on a Bruker DRX-400 spectrometer operating at 160 MHz. High-resolution mass spectrometry (HRMS) was recorded on a LCT Premier Spectrometer (Micromass UK Limited) operating on ESI-positive mode (MeOH) and reported for the parent molecule [$(RO)_3P$-$BH_3$], the corresponding phosphite fragment [$(RO)_3P$], or the oxidized parent molecule

$[(RO)_3P{=}O]$.[1] HRMS spectra for thiophosphate **3.10.4** was acquired on a Q-Tof-2 (Micromass Ltd ,Manchester UK) hybrid mass spectrometer operated in MS mode and acquiring data with the time of flight analyzer (Hexanes APCI-MS). Observed rotations at 589 nm, were measured using AUTOPOL IV Model automatic polarimeter. IR was recorded on Shimadzu FTIR-8400S instrument.

### 5.2.2 Experimental Section

**(4*S*,6*S*)-2-(allyloxy)-4,6-divinyl-1,3,2-dioxaphosphite 1-borane ($C_{10}H_{18}BO_3P$, 3.9.2)**




**3.9.2**

In the glovebox (under argon) was added allyl tetraisopropylphosphorodiamidite (0.926 g, 4.06 mmol) to an oven-dried round bottom flask equipped with a magnetic stirbar. The flask was capped with a rubber septum, removed from the glovebox, and equipped with an argon inlet. To the phosphorodiamidite, under argon, was added dry, degassed acetonitrile (25 mL), then 1*H*-tetrazole (0.481 g, 6.87 mmol), and the mix stirred at room temperature for 10 minutes (white solids formed and the mix became heterogeneous). To

[1] For many of the bicyclic phosphite-borane molecules reported in this publication, the fragmentation pattern resulting from electrospray ionization was complex, though typically the phosphite fragment m/z, the parent molecule m/z, and/or the oxidized form (phosphate) m/z were observed (in ranges of 2–20 ppm difference from the calculated mass). In these cases, the microgram scale oxidation of the phosphite-borane was carried out via the deprotection-oxidation protocol reported below (see preparation of **3.10.3**), and HRMS recorded for the resultant phosphate (crude).

the stirring mixture was added (3*S*,5*S*)-hepta-1,6-diene-3,5-diol[2] (**3.9.1**, 0.400 g, 3.12 mmol) in acetonitrile (6.2 mL), dropwise. The heterogeneous mix stirred at room temperature for 3.5 hours (complete by TLC), and $BH_3$•THF (9.4 mL, 1.0 M in THF) was added dropwise over 5 minutes (Note: the reaction cleared during addition of borane-THF complex). The reaction stirred at room temperature for 1 hour (complete by TLC), where excess borane was quenched by the addition of $H_2O$ (~10 mL) and the mix was concentrated under reduced pressure to 1/3 its original volume. The cloudy solution was partitioned between equal portions of EtOAc and water (30 mL:30 mL), and the biphasic solution was separated. The aqueous layer was extracted with EtOAc (3 x 20 mL), and the organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude mix was purified by flash, filter column (silica, 15% EtOAc in hexanes) to provide clean triene **3.9.2** (0.514 g, 2.26 mmol, 72% yield) as a clear, colorless liquid. Note: Extended column times resulted in partial triene decomposition, even with the addition of triethylamine to column eluent (5-10%). The triene was stored under argon in the freezer for extended store times.

**FTIR** (neat): 3088, 2934, 2401, 1425, 1120, 1096, 1005, 987, 926, 852, 729, 663 $cm^{-1}$;

**Optical Rotation**: $[\alpha]_D$ = +93.9 (*c* = 0.17, $CHCl_3$);

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.10 (ddd, *J* = 17.1, 10.5, 6.5 Hz, 1H, $CH_2$=C<u>H</u>–), 5.98–5.85 (m, 2H, $CH_2$=C<u>H</u>–, $CH_2$=C<u>H</u>–), 5.45 (dt, *J* = 17.1, 1.3 Hz, 1H, C<u>H$_a$</u>H$_b$=CH–), 5.38 (dt, *J* = 3.4, 1.4 Hz, 1H, C<u>H$_a$</u>H$_b$=CH–), 5.35 (dt, *J* = 3.3, 1.4 Hz, 1H, C<u>H$_a$</u>H$_b$=CH–), 5.32

[2] Rychnovsky, S. D.; Griesgraber, G.; Powers, J. P. *Org. Synth.* **2000**, *77*, 1–11.

(dd, $J$ = 1.3, 1.3 Hz, 1H, $CH_a\underline{H}_b$=CH–), 5.30 (dd, $J$ = 1.3, 1.3 Hz, 1H, $CH_a\underline{H}_b$=CH–), 5.26 (dd, $J$ = 10.4, 1.4 Hz, 1H, $CH_a\underline{H}_b$=CH–), 5.02 (dqt, $J$ = 8.8, 3.5, 1.7 Hz, 1H, $CH_2$=CH-C$\underline{H}$-O(P)-$CH_2$–), 4.93 (dddd, $J$ = 13.1, 6.5, 5.0, 3.5 Hz, 1H, $CH_2$=CH-C$\underline{H}$-O(P)-$CH_2$–), 4.54 (tdd, $J$ = 7.2, 3.5, 1.5 Hz, 2H, (P)-O-C$\underline{H}_2$-CH=$CH_2$), 2.25 (dddd, $J$ = 14.7, 8.4, 5.0, 1.2 Hz, 1H, $CH_2$=CH-CH-O(P)-C$\underline{H}_a$$H_b$-O(P)-CH–), 2.15 (dddd, $J$ = 14.7, 5.1, 3.5, 1.7 Hz, 1H, $CH_2$=CH-CH-O(P)-$CH_a\underline{H}_b$-O(P)-CH–), 0.85 – 0.19 (m, 3H, -B$\underline{H}_3$).

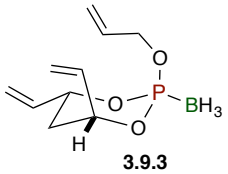
**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 135.6 (d, $J_{CP}$ = 1.5 Hz, CH), 135.1 (d, $J_{CP}$ = 5.7 Hz, CH), 132.5 (d, $J_{CP}$ = 6.1 Hz, CH), 118.3 ($CH_2$), 118.1 ($CH_2$), 117.5 ($CH_2$), 76.3 (d, $J_{CP}$ = 9.5 Hz, CH), 72.3 (d, $J_{CP}$ = 7.8 Hz, CH), 67.5 ($CH_2$), 35.5 (d, $J_{CP}$ = 9.3 Hz, $CH_2$);

**$^{31}$P NMR** (162 MHz, $CDCl_3$) δ 110.8 – 108.4 (short, br, m);

**$^{11}$B NMR** (160 MHz, $CDCl_3$) δ -42.5 (dq, $J$ = 98.1, 98.1 Hz);

**HRMS** cald for oxidized parent molecule $C_{10}H_{15}O_4PNa$ $(M+Na)^+$ 253.0606; found 253.0610 (TOF MS ES+).

**(4*R*,6*R*)-2-(allyloxy)-4,6-divinyl-1,3,2-dioxaphosphite 1-borane ($C_{10}H_{18}BO_3P$, 3.9.3)**




3.9.3

In the glovebox (under argon) was added allyl tetraisopropylphosphorodiamidite (0.852 g, 3.74 mmol) to an oven-dried round bottom flask equipped with a magnetic stirbar. The flask was capped with a rubber septum, removed from the glovebox, and equipped with an argon inlet. To the phosphorodiamidite, under argon, was added dry, degassed

acetonitrile (21 mL), then 1H-tetrazole (0.443 g, 6.32 mmol), and the mix stirred at room temperature for 10 minutes (white solids formed and the mix became heterogeneous). To the stirring mixture was added (3*R*,5*R*)-hepta-1,6-diene-3,5-diol[2] (**3.9.1**, 0.368 g, 2.87 mmol) in acetonitrile (8 mL), dropwise. The heterogeneous mix stirred at room temperature for 3.5 hours (complete by TLC), and $BH_3$•THF (8.6 mL, 1.0 M in THF) was added dropwise over 5 minutes (Note: the reaction cleared during addition of borane-THF complex). The reaction stirred at room temperature for 1 hour (complete by TLC), where excess borane was quenched by the addition of $H_2O$ (~10 mL) and the mix was concentrated under reduced pressure to 1/3 its original volume. The cloudy solution was partitioned between equal portions of EtOAc and water (30 mL:30 mL), and the biphasic solution was separated. The aqueous layer was extracted with EtOAc (3 x 20 mL), and the organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude mix was purified by flash, filter column (silica, 15% EtOAc in hexanes) to provide clean triene **3.9.3** (0.479 g, 2.10 mmol, 73% yield) as a clear, colorless liquid. Note: Extended column times resulted in partial triene decomposition, even with the addition of triethylamine to column eluent (5-10%). The triene was stored under argon in the freezer for extended store times.

**FTIR** (neat): 3086, 2930, 2399, 1425, 1409, 1124, 1005, 987, 926, 852, 729, 663 $cm^{-1}$;

**Optical Rotation**: $[\alpha]_D = -89.0$ (*c* = 0.39, $CHCl_3$);

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.10 (ddd, *J* = 17.1, 10.5, 6.5 Hz, 1H, $CH_2$=C<u>H</u>–), 5.99–5.85 (m, 2H, $CH_2$=C<u>H</u>–, $CH_2$=C<u>H</u>–), 5.45 (dt, *J* = 17.1, 1.2 Hz, 1H, C<u>H$_a$</u>H$_b$=CH–), 5.39

(p, $J$ = 1.4 Hz, 1H, C$\underline{H}_a$H$_b$=CH–), 5.35 (p, $J$ = 1.4 Hz, 1H, C$\underline{H}_a$H$_b$=CH–), 5.33 (q, $J$ = 1.1 Hz, 1H, C$\underline{H}_a$H$_b$=CH–), 5.30 (q, $J$ = 1.1 Hz, 1H, C$\underline{H}_a$H$_b$=CH–), 5.26 (dd, $J$ = 10.4, 1.4 Hz, 1H, C$\underline{H}_a$H$_b$=CH–), 5.02 (dqd, $J$ = 8.7, 3.7, 1.9 Hz, 1H, CH$_2$=CH-C$\underline{H}$-O(P)-CH$_2$–), 4.93 (dddd, $J$ = 13.1, 6.5, 5.0, 3.5 Hz, 1H, CH$_2$=CH-CH-O(P)-C$\underline{H}_a$H$_b$-O(P)-CH–), 4.55 (dtt, $J$ = 8.5, 5.9, 1.4 Hz, 2H, (P)-O-C$\underline{H}_2$-CH=CH$_2$), 2.25 (dddd, $J$ = 14.7, 8.5, 5.0, 1.1 Hz, 1H, CH$_2$=CH-CH-O(P)-C$\underline{H}_a$H$_b$-O(P)-CH–), 2.15 (dddd, $J$ = 14.7, 5.1, 3.5, 1.6 Hz, 1H, CH$_2$=CH-CH-O(P)-CH$_a$$\underline{H}_b$-O(P)-CH–), 0.88 – 0.19 (m, 3H, -B$\underline{H}_3$).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 135.6 (d, $J_{CP}$ = 1.6 Hz, CH), 135.2 (d, $J_{CP}$ = 5.9 Hz, CH), 132.5 (d, $J_{CP}$ = 6.2 Hz, CH), 118.3 ($CH_2$), 118.2 ($CH_2$), 117.6 ($CH_2$), 76.3 (d, $J_{CP}$ = 9.3 Hz, CH), 72.3 (d, $J_{CP}$ = 7.8 Hz, CH), 67.6 ($CH_2$), 35.5 (d, $J_{CP}$ = 9.2 Hz, $CH_2$);

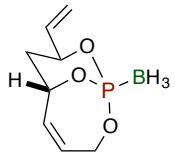
**$^{31}$P NMR** (162 MHz, $CDCl_3$) δ 113.3 – 106.8 (short, br, m);

**$^{11}$B NMR** (160 MHz, $CDCl_3$) δ -42.6 (dq, $J$ = 98.2, 98.2 Hz);

**HRMS** cald for oxidized parent molecule $C_{10}H_{15}O_4PNa$ $(M+Na)^+$ 253.0606; found 253.0603 (TOF MS ES+).

**(1*S*,6*S*,8*S*)-8-vinyl-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-borane**

**($C_8H_{14}BO_3P$, 3.9.4)**




($S_P$,*S*,*S*)-**3.9.4**

To an oven-dried, round bottom flask equipped with a reflux condenser and magnetic stirbar, under argon, was added triene **3.9.2** (0.420 g, 1.84 mmol), methylene chloride (dry, degassed, 263 mL), and $(ImesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$[3] (G-II, 47.0 mg, 0.055 mmol, 3 mol %), sequentially. The flask was heated to reflux and stirred at reflux for 2 hours (complete by TLC). The solvent was removed under reduced pressure, and the crude mix was purified via flash chromatography (silica, 0% - 50% EtOAc in hexanes) to provide bicyclic phosphite-borane **3.9.4** (0.306 g, 1.53 mmol, 83% yield) as an off-white solid.[4] Note: the bicyclic phosphite-borane can be stored for extended periods of time (>2 years) at lower temperatures (<5 $^oC$). Some decomposition was observed for samples stored at ambient temperature for greater than 1 month.

**Avg. Yield:** 81–85%

**M.P.** 103–104 $^oC$

**FTIR** (neat): 2995, 2937, 2424, 2394, 1418, 1394, 1259, 1236, 1081, 1045, 1020, 991, 943, 912, 871, 787, 771, 731, 656, 608 $cm^{-1}$;

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[3] Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.
[4]All X-ray crystallographic data has been submitted to the Cambridge Crystallographic Data Centre, and the structures for this work were assigned the following deposition numbers: ($R_P$,*R*,*R*)-**3.9.5** [1484372] and ($S_P$,*S*,*S*)-**3.9.4** [1484373].

**Optical Rotation**: $[\alpha]_D$ = + 148. (*c* = 0.90, $CHCl_3$);

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.08 (dddd, *J* = 11.7, 6.6, 3.2, 1.9 Hz, 1H, (P)O-CH-CH=C<u>H</u>-$CH_2$-O(P)), 5.86 (ddd, *J* = 17.2, 10.6, 5.7 Hz, 1H, -C<u>H</u>=$CH_2$), 5.66 (ddd, *J* = 11.6, 4.0, 2.6 Hz, 1H, (P)O-CH-C<u>H</u>=CH-$CH_2$-O(P)), 5.40 (dt, *J* = 17.1, 1.2 Hz, 1H, -CH=C<u>H</u>$_a$H$_b$), 5.28 (dt, *J* = 10.6, 1.2 Hz, 1H, -CH=CH$_a$<u>H</u>$_b$), 5.19 (dddt, *J* = 16.0, 6.0, 4.0, 2.0 Hz, 1H, (P)O-C<u>H</u>-CH=CH-$CH_2$-O(P)), 5.05 – 4.99 (m, 1H, -$CH_2$-(P)O-C<u>H</u>-CH=$CH_2$), 4.92 (dddd, *J* = 14.8, 5.7, 3.9, 2.6 Hz, 1H, (P)O-C<u>H</u>$_a$H$_b$-CH=CH-), 4.45 (ddd, *J* = 22.9, 14.7, 6.6 Hz, 1H, (P)O-CH$_a$<u>H</u>$_b$-CH=CH-), 2.40 (ddd, *J* = 14.7, 12.0, 6.0 Hz, 1H, (P)O-CH-C<u>H</u>$_a$H$_b$-CH-O(P)), 1.85 (dq, *J* = 14.6, 1.8 Hz, 1H, (P)O-CH-CH$_a$<u>H</u>$_b$-CH-O(P)), 0.86 – 0.17 (m, 3H, -B<u>H</u>$_3$);

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 135.0 (d, $J_{CP}$ = 7.3 Hz, CH), 130.8 (CH), 128.8 (CH), 117.8 (d, $J_{CP}$ = 1.8 Hz, $CH_2$), 77.4 (d, $J_{CP}$ = 8.8 Hz, CH), 70.7 (d, $J_{CP}$ = 6.9 Hz, CH), 63.4 (d, $J_{CP}$ = 8.1 Hz, $CH_2$), 35.6 (d, $J_{CP}$ = 5.9 Hz, $CH_2$);

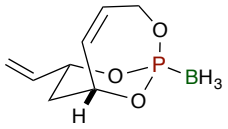
**$^{31}$P NMR** (162 MHz, $CDCl_3$) δ 112.8 (short, d (br), *J* = 124.8 Hz);

**$^{11}$B NMR** (160 MHz, $CDCl_3$) δ -42.7 (dq, *J* = 98.5, 98.5 Hz);

**HRMS** cald for oxidized parent molecule $C_8H_{11}O_4PNa$ $(M+Na)^+$ 225.0293; found 225.0300 (TOF MS ES+).

**(1*R*,6*R*,8*R*)-8-vinyl-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-borane**

**($C_8H_{14}BO_3P$, 3.9.5)**




($R_P$,*R*,*R*)-**3.9.5**

To an oven-dried, round bottom flask equipped with a reflux condenser and magnetic stirbar, under argon, was added triene **3.9.3** (0.420 g, 1.84 mmol), methylene chloride (dry, degassed, 263 mL), and $(ImesH_2)(PCy_3)(Cl)_2Ru$=CHPh (G-II, 47.0 mg, 0.055 mmol, 3 mol %), sequentially. The flask was heated to reflux and stirred at reflux for 2 hours (complete by TLC). The solvent was removed under reduced pressure, and the crude mix was purified via flash chromatography (silica, 0% - 50% EtOAc in hexanes) to provide bicyclic phosphite-borane **3.9.5** (0.306 g, 1.53 mmol, 83% yield) as an off-white solid.[4] Note: the bicyclic phosphite-borane can be stored for extended periods of time (>2 years) at lower temperatures (<5 $^oC$). Some decomposition was observed for samples stored at ambient temperature for greater than 1 month.

**Avg. Yield:** 81–85%

**M.P.** 102–103 $^oC$

**FTIR** (neat): 2995,2937, 2424, 2394, 1458, 1429, 1418, 1394, 1259, 1236, 1082, 1045, 1020, 991, 943, 912, 831, 787, 771, 658, 579 $cm^{-1}$;

**Optical Rotation**: $[\alpha]_D = -146$. (*c* = 0.68, $CHCl_3$);

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.08 (dddd, *J* = 11.7, 6.6, 3.2, 2.0 Hz, 1H, (P)O-CH-CH=C<u>H</u>-$CH_2$-O(P)), 5.86 (ddd, *J* = 17.2, 10.6, 5.7 Hz, 1H, -C<u>H</u>=$CH_2$), 5.66 (ddd, *J* =

11.6, 4.0, 2.6 Hz, 1H, (P)O-CH-C<u>H</u>=CH-$CH_2$-O(P)), 5.40 (dt, *J* = 17.1, 1.2 Hz, 1H, -CH=C<u>H</u>$_a$H$_b$), 5.28 (dt, *J* = 10.6, 1.1 Hz, 1H, -CH=CH$_a$<u>H</u>$_b$), 5.19 (dtt, *J* = 15.9, 4.0, 2.0 Hz, 1H, (P)O-C<u>H</u>-CH=CH-$CH_2$-O(P)), 5.05 – 4.99 (m, 1H, -$CH_2$-(P)O-C<u>H</u>-CH=$CH_2$), 4.92 (ddq, *J* = 14.8, 4.0, 2.6 Hz, 1H, (P)O-C<u>H</u>$_a$H$_b$-CH=CH-), 4.45 (ddd, *J* = 22.7, 14.8, 6.6 Hz, 1H, (P)O-CH$_a$<u>H</u>$_b$-CH=CH-), 2.40 (ddd, *J* = 14.6, 12.0, 6.0 Hz, 1H, (P)O-CH-C<u>H</u>$_a$H$_b$-CH-O(P)), 1.84 (dq, *J* = 14.6, 1.8 Hz, 1H, (P)O-CH-CH$_a$<u>H</u>$_b$-CH-O(P)), 0.87 – 0.17 (m, 3H, -B<u>H</u>$_3$);

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 135.0 (d, $J_{CP}$ = 7.3 Hz, CH), 130.8 (CH), 128.8 (CH), 117.8 ($CH_2$), 77.4 (d, $J_{CP}$ = 8.9 Hz, CH), 70.7 (d, $J_{CP}$ = 6.9 Hz, CH), 63.4 (d, $J_{CP}$ = 8.1 Hz, $CH_2$), 35.6 (d, $J_{CP}$ = 5.8 Hz, $CH_2$);

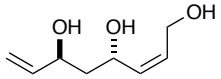
**$^{31}$P NMR** (162 MHz, $CDCl_3$) δ 112.9 (short, d (br), *J* = 147.8 Hz);

**$^{11}$B NMR** (160 MHz, $CDCl_3$) δ -42.7 (dq, *J* = 98.8, 98.8 Hz);

**HRMS** cald for oxidized parent molecule $C_8H_{11}O_4PNa$ $(M+Na)^+$ 225.0293; found 225.0295 (TOF MS ES+).

**(4*S*,6*S*,*Z*)-octa-2,7-diene-1,4,6-triol ($C_8H_{14}O_3$, 3.10.1)**

**3.10.1**




To a stirring solution of ($S_P$,*S*,*S*)-bicyclic phosphite-borane **3.9.4** (40 mg, 0.20 mmol) in toluene (2 mL) under argon was added Red-Al [0.3 mL, 65% wt.% in toluene], dropwise, at 0 $^oC$. The reaction was allowed to warm to room temperature in the ice bath and stirred

at room temperature overnight (complete by TLC). The reaction was quenched with saturated sodium potassium tartrate (aq, 1 mL), and the reaction stirred at room temperature until clear, separable layers formed (~30 minutes). The biphasic solution was separated, and the aqueous layer was neutralized with 1 M HCl (aq) [monitored with pH paper] and then extracted with EtOAc [4 x 2 mL] and n-butanol [3 x 2 mL]. The organic layers were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude mix was purified via flash chromatography (silica, 50%–100% EtOAc in hexanes) to afford triol **3.10.1** (24.3 mg, 0.15 mmol, 77% yield) as a colorless oil. All data was in agreement with previous reports.[5]

**$^{1}$H NMR** (500 MHz, $CDCl_3$) δ 5.94 (ddd, *J* = 17.2, 10.4, 5.5 Hz, 1H), 5.75 (dddd, *J* = 11.3, 6.8, 5.8, 1.2 Hz, 1H), 5.66 (dddd, *J* = 11.3, 7.5, 1.3, 1.3 Hz, 1H), 5.32 (ddd, *J* = 17.2, 1.5, 1.5 Hz, 1H), 5.18 (ddd, *J* = 10.5, 1.4, 1.4 Hz, 1H), 4.80 (td, *J* = 7.7, 3.1 Hz, 1H), 4.56 – 4.45 (m, 1H), 4.30 (dd, *J* = 13.3, 6.9 Hz, 1H), 4.20 (dd, *J* = 13.2, 5.8 Hz, 1H), 3.06 (s, 1H), 2.53 (d, *J* = 4.3 Hz, 1H), 2.19 (s, 1H), 1.89 (ddd, *J* = 14.5, 8.5, 3.6 Hz, 1H), 1.72 (ddd, *J* = 14.5, 7.6, 3.4 Hz, 1H);

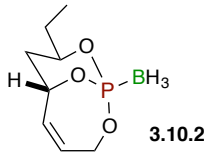
**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 140.2, 134.8, 130.0, 114.8, 70.6, 65.7, 58.7, 42.4;

**HRMS** cald for $C_8H_{14}O_3Na$ $(M+Na)^+$ 181.0841; found 181.0847 (TOF MS ES+).

[5] Whitehead, A.; McReynolds, M. D.; Moore, J. D.; Hanson, P. R. *Org. Lett.* **2005**, *7*, 3375–3378.

**(1*S*,6*S*,8*R*)-8-ethyl-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-borane**

**($C_8H_{16}BO_3P$, 3.10.2)**




3.10.2

To a solution of ($S_P$,*S*,*S*)-bicyclic phosphite-borane **3.9.4** (40 mg, 0.20 mmol) in methylene chloride (4 mL) was added *o*-nitrobenzenesulfonylhydrazide (0.43 g, 2.0 mmol) and triethylamine (0.9 mL) at room temperature under argon. The flask was protected from light (covered with aluminum foil) and allowed to stir at room temperature for 12 hours, at which point additional *o*-nitrobenzenesulfonylhydrazide[6] (0.22 g, 1.0 mmol) and triethylamine (0.45 mL) were added to the mixture. The reaction continued to stir at room temperature for 10 hours, at which point the solution was diluted with EtOAc (10 mL) and washed with saturated sodium bicarbonate (2 x 2 mL). The aqueous layers were combined and extracted with EtOAc (3 x 10 mL), and the organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude mix was purified via flash chromatography to provide **3.10.2** (29 mg, 0.14 mmol, 72% yield) as an off-white solid.

**FTIR** (neat): 2970, 2933, 2881, 2403, 1462, 1396, 1360, 1259, 1097, 1059, 1024, 991, 957, 941, 908, 870, 833, 779, 660 $cm^{-1}$;

**Optical Rotation**: $[\alpha]_D$ = +150. (*c* = 1.21, $CHCl_3$);

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[6] Myers, A. G.; Zheng, B.; Movassaghi, M. *J. Org. Chem.* **1997**, *62*, 7507.

**$^{1}$H NMR** (500 MHz, $CDCl_3$) δ 6.05 (dddd, *J* = 11.7, 6.7, 3.2, 2.0 Hz, 1H, -C<u>H</u>=CH-), 5.63 (ddd, *J* = 11.6, 4.0, 2.7 Hz, 1H, -C<u>H</u>=CH-), 5.16 (dtt, *J* = 16.0, 4.0, 1.9 Hz, 1H, -$CH_2$-(P)O-C<u>H</u>-$CH_2CH_3$), 4.93 – 4.87 (m, 1H, (P)O-C<u>$H_a$</u>$H_b$-CH=CH-), 4.52 – 4.35 (m, 2H, (P)O-$CH_a$<u>$H_b$</u>-CH=CH-, -$CH_2$-(P)O-C<u>H</u>-CH=CH-), 2.30 (ddd, *J* = 14.6, 11.9, 6.1 Hz, 1H, O(P)-CH-C<u>$H_a$</u>$H_b$-CH-O(P)), 1.81 – 1.69 (m, 2H, O(P)-CH-$CH_a$<u>$H_b$</u>-CH-O(P), -C<u>$H_a$</u>$H_b$$CH_3$), 1.66 – 1.56 (m, 1H, -$CH_a$<u>$H_b$</u>$CH_3$), 0.98 (t, *J* = 7.5 Hz, 3H, -$CH_2$-C<u>$H_3$</u>), 0.82 – 0.16 (m, 3H, -B<u>$H_3$</u>);

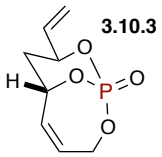
**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 131.1 (CH), 128.5 (CH), 77.6 (d, $J_{CP}$ = 8.8 Hz, CH), 72.2 (d, $J_{CP}$ = 7.2 Hz, CH), 63.3 (d, $J_{CP}$ = 8.1 Hz, $CH_2$), 35.2 (d, $J_{CP}$ = 5.9 Hz, $CH_2$), 28.8 (d, $J_{CP}$ = 6.5 Hz, $CH_2$), 9.0 ($CH_3$);

**$^{31}$P NMR** (162 MHz, $CDCl_3$) δ 112.5 (short, d (br), *J* = 124.6 Hz);

**$^{11}$B NMR** (160 MHz, $CDCl_3$) δ -42.7 (dq, *J* = 98.7, 98.7 Hz);

**HRMS** cald for oxidized parent molecule $C_8H_{13}O_4PNa$ $(M+Na)^+$ 227.0449; found 227.0439 (TOF MS ES+).

**(1*S*,6*S*,8*S*)-8-vinyl-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-oxide ($C_8H_{11}O_4P$, 3.10.3)**




To ($S_P$,*S*,*S*)-bicyclic phosphite-borane **3.9.4** (30.0 mg, 0.150 mmol) in a pressure tube under argon was added dry, degassed toluene (1.9 mL) and 1,4-diazabicyclo[2.2.2]octane [DABCO] (16.8 mg, 0.150 mmol). The tube was capped and heated to 60 $^oC$ and stirred for 2 hours (phosphite formation was complete by TLC, $R_f$ = 0.84 in 1:1 hexanes:EtOAc). The reaction was cooled to room temperature, where tBuOOH (21 mL, 70% wt.% in $H_2O$) was added in one portion via automatic micropipette and the reaction stirred at room temperature open to air for 1 hour (complete by TLC, Note: If the oxidation of phosphite to phosphate is incomplete—as sometimes happens, particularly with other substrates, an additional 0.1-0.2 equivalents of tBuOOH can be added without substantial oxidation of the olefins within the substrate. Significant excess of peroxide, however, does lead to product decomposition). The reaction was subsequently quenched with solid sodium sulfite, allowed to stir at room temperature to ensure consumption of excess peroxide, filtered over celite, and concentrated under reduced pressure. The crude mix was purified via flash chromatography to provide the corresponding bicyclic phosphate **3.10.3** (30.3 mg, 0.150 mmol, quantitative yield) as a white solid. All data was in agreement with previous reports.[5]

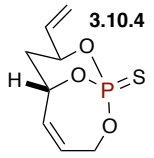
**$^{1}$H NMR** (500 MHz, $CDCl_3$) δ 6.06 (dddd, *J* = 12.0, 6.8, 3.2, 2.1 Hz, 1H, (P)O-CH-CH=C<u>H</u>-$CH_2$-O(P)), 5.87 (dddd, *J* = 17.1, 10.6, 5.4, 2.0 Hz, 1H, -C<u>H</u>=$CH_2$), 5.63 (ddd, *J* = 11.8, 4.0, 2.5 Hz, 1H, (P)O-CH-C<u>H</u>=CH-$CH_2$-O(P)), 5.43 (ddd, *J* = 17.2, 1.2, 1.2 Hz, 1H, -CH=C<u>H$_a$H$_b$</u>), 5.27 (ddd, *J* = 10.6, 1.1, 1.1 Hz, 1H, -CH=CH$_a$<u>H$_b$</u>), 5.21 (dtd, *J* = 24.5, 4.2, 2.1 Hz, 1H, (P)O-C<u>H</u>-CH=CH-$CH_2$-O(P)), 5.07 – 4.97 (m, 2H, -$CH_2$-(P)O-C<u>H</u>-$CH=CH_2$, (P)O-C<u>H$_a$H$_b$</u>-CH=CH-), 4.39 (ddd, *J* = 27.7, 14.7, 6.7 Hz, 1H, (P)O-CH$_a$<u>H$_b$</u>-CH=CH-), 2.28 – 2.20 (m, 1H, (P)O-CH-C<u>H$_a$H$_b$</u>-CH-O(P)), 1.81 (dtd, *J* = 14.7, 2.3, 1.4 Hz, 1H, (P)O-CH-CH$_a$<u>H$_b$</u>-CH-O(P));

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 134.7 (d, $J_{CP}$ = 10.4 Hz, CH), 129.6 (CH), 128.1 (CH), 117.4 ($CH_2$), 76.96 (d, $J_{CP}$ = 4.99 Hz, CH), 76.2 (d, $J_{CP}$ = 6.2 Hz, CH), 63.0 (d, $J_{CP}$ = 6.4 Hz, $CH_2$), 34.9 (d, $J_{CP}$ = 5.8 Hz, $CH_2$);

**$^{31}$P NMR** (162 MHz, $CDCl_3$) δ -4.21;

**HRMS** cald for $C_8H_{11}O_4PNa$ $(M+Na)^+$ 225.0293; found 225.0288 (TOF MS ES+).

**(1*R*,6*S*,8*S*)-8-vinyl-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-sulfide ($C_8H_{11}O_3PS$, 3.10.4)**




To (*S*$_P$,*S*,*S*)-bicyclic phosphite-borane **3.9.4** (30.0 mg, 0.150 mmol) in a pressure tube under argon was added dry, degassed toluene (2.5 mL), 1,4-diazabicyclo[2.2.2]octane [DABCO] (16.8 mg, 0.150 mmol), and elemental sulfur (16.8 mg, 0.150 mmol). The tube

was capped and heated to 60 $^{o}$C and stirred for 10 hours (complete by TLC). The reaction was concentrated, and the crude mixture immediately purified via flash chromatography (silica, 0%–50% EtOAc in hexanes) to afford bicyclic thiophosphate **3.10.4** (32.0 mg, 0.147 mmol, 98% yield) as an off-white solid.

**FTIR** (neat): 2993, 2964, 2933, 1427. 1394, 1258, 1236, 1084, 1051, 1026, 941, 910, 872, 841, 827, 750, 739, 677, 584 cm$^{-1}$;

**Optical Rotation**: $[\alpha]_D$ = +165 (*c* = 0.15, $CHCl_3$);

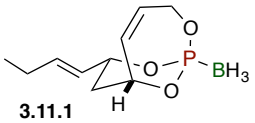
**$^{1}$H NMR** (500 MHz, $CDCl_3$) δ 6.07 (dddd, *J* = 11.7, 6.6, 3.1, 2.0 Hz, 1H, (P)O-CH-CH=C<u>H</u>-$CH_2$-O(P)), 5.90 (dddd, *J* = 17.5, 10.6, 5.8, 1.3 Hz, 1H, -C<u>H</u>=$CH_2$), 5.62 (ddd, *J* = 11.7, 4.1, 2.6 Hz, 1H, (P)O-CH-C<u>H</u>=CH-$CH_2$-O(P)), 5.42 (dt, *J* = 17.2, 1.2 Hz, 1H, -CH=C<u>H</u>$_a$H$_b$), 5.29 (dt, *J* = 10.6, 1.1 Hz, 1H, -CH=CH$_a$<u>H</u>$_b$), 5.21 (dtt, *J* = 23.8, 4.3, 2.0 Hz, 1H, (P)O-C<u>H</u>-CH=CH-$CH_2$-O(P)), 5.14 – 5.06 (m, 1H, -$CH_2$-(P)O-C<u>H</u>-CH=$CH_2$), 5.02 (ddq, *J* = 14.8, 7.3, 2.7 Hz, 1H, (P)O-C<u>H</u>$_a$H$_b$-CH=CH-), 4.41 (ddd, *J* = 28.3, 14.8, 6.6 Hz, 1H, (P)O-CH$_a$<u>H</u>$_b$-CH=CH-), 2.38 – 2.30 (m, 1H, (P)O-CH-C<u>H</u>$_a$H$_b$-CH-O(P)), 1.82 (dddd, *J* = 14.7, 3.2, 2.1, 1.3 Hz, 1H, (P)O-CH-CH$_a$<u>H</u>$_b$-CH-O(P));

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 134.9 (d, $J_{CP}$ = 10.0 Hz, CH), 129.9 (CH), 128.3 (CH), 118.0 ($CH_2$), 78.1 (d, $J_{CP}$ = 9.1 Hz, CH), 75.7 (d, $J_{CP}$ = 8.1 Hz, CH), 62.9 (d, $J_{CP}$ = 7.4 Hz, $CH_2$), 34.7 (d, $J_{CP}$ = 6.4 Hz, $CH_2$);

**$^{31}$P NMR** (162 MHz, $CDCl_3$) δ 64.8 (ddd, *J* = 28.2, 24.5, 7.4 Hz);

**HRMS** cald for $C_8H_{12}O_3PS$ $(M+H)^+$ 219.0245; found 219.0246 (Hexanes APCI-MS, ES+).

**(1*R*,6*R*,8*R*)-8-((*E*)-but-1-en-1-yl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-borane ($C_{10}H_{18}BO_3P$, 3.11.1)**




**3.11.1**

To a solution of ($R_P$,*R*,*R*)-bicyclic phosphite-borane **3.9.5** (30.0 mg, 0.150 mmol) in a pressure tube under argon was added dry, degassed methylene chloride (1.9 mL), *cis*-3-hexene (20 mL, 0.165 mmol), then Hoveyda-Grubbs second generation catalyst (4.7 mg, 0.0075 mmol, 5 mol %). The pressure tube was capped, and the reaction was heated to 40 $^oC$. The reaction stirred at 40 $^oC$ for 2 hours (complete by TLC) and then concentrated under reduced pressure. The crude mixture was purified via flash chromatography (silica, 0%–50% EtOAc in hexanes) to provide title **3.11.1** (29.7 mg, 0.130 mmol, 87% yield) as an off-white solid.

**FTIR** (neat): 2964, 2930, 2881, 2403, 2357, 1460, 1397, 1259, 1117, 1091, 1072, 1045, 1028, 995, 943, 916, 867, 831, 789, 667, 619, 582 $cm^{-1}$;

**Optical Rotation**: $[\alpha]_D = -155$ (*c* = 0.65, $CHCl_3$);

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.07 (dddd, *J* = 11.7, 6.6, 3.1, 1.9 Hz, 1H, (P)O-CH-CH=C<u>H</u>-$CH_2$-O(P)), 5.88 (dtd, *J* = 15.5, 6.3, 1.1 Hz, 1H, -CH=C<u>H</u>-$CH_2CH_3$), 5.65 (ddd, *J* = 11.6, 4.0, 2.6 Hz, 1H, (P)O-CH-C<u>H</u>=CH-$CH_2$-O(P)), 5.50 (ddt, *J* = 15.4, 7.0, 1.7 Hz, 1H, -C<u>H</u>=CH-$CH_2CH_3$), 5.17 (dtt, *J* = 15.9, 3.9, 1.9 Hz, 1H, (P)O-C<u>H</u>-CH=CH-$CH_2$-O(P)), 5.01 – 4.94 (m, 1H, -$CH_2$-(P)O-C<u>H</u>-CH=CH-$CH_2$-$CH_3$), 4.95 – 4.88 (m, 1H, (P)O-C<u>H$_a$H$_b$</u>-CH=CH-), 4.44 (ddd, *J* = 22.8, 14.8, 6.7 Hz, 1H, (P)O-CH$_a$<u>H$_b$</u>-CH=CH-), 2.42

(ddd, $J$ = 14.7, 11.9, 6.1 Hz, 1H, (P)O-CH-C$\underline{H}_a$H$_b$-CH-O(P)), 2.12 – 2.05 (m, 2H, -CH=CH-C$\underline{H}_2$-CH$_3$), 1.80 (dq, $J$ = 14.6, 1.8 Hz, 1H, (P)O-CH-CH$_a\underline{H}_b$-CH-O(P)), 1.01 (t, $J$ = 7.5 Hz, 3H, -CH=CH-C$\underline{H}_2$-CH$_3$), 0.90 – 0.10 (m, 3H, -BH$_3$);

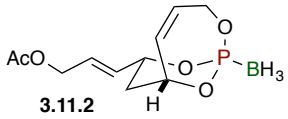
**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 137.4 (CH), 130.9 (CH), 128.7 (CH), 126.1 (d, $J_{CP}$ = 7.3 Hz, CH), 77.45 (d, $J_{CP}$ = 8.9 Hz, CH), 71.3 (d, $J_{CP}$ = 6.8 Hz, CH), 63.3 (d, $J_{CP}$ = 7.9 Hz, $CH_2$), 36.1 (d, $J_{CP}$ = 5.7 Hz, $CH_2$), 25.1 ($CH_2$), 12.9 ($CH_3$);

**$^{31}$P NMR** (162 MHz, $CDCl_3$) δ 112.7 (short, d (br), $J$ = 156.3 Hz);

**$^{11}$B NMR** (160 MHz, $CDCl_3$) δ -42.7 (dq, $J$ = 95.9, 93.5 Hz);

**HRMS** cald for oxidized parent molecule $C_{20}H_{30}O_8P_2Na$ $(2M+Na)^+$ 483.1314; found 483.1321 (TOF MS ES+).

**(*E*)-3-((1*R*,6*R*,8*R*)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl)allyl acetate 1-borane ($C_{11}H_{18}BO_5P$, 3.11.2)**



**3.11.2**

To a solution of ($R_P$,*R*,*R*)-bicyclic phosphite-borane **3.9.5** (30.0 mg, 0.150 mmol) in a pressure tube under argon was added dry, methylene chloride (1.9 mL, degassed via 3 freeze-degas-thaw cycles), cis-1,4-diacetoxy-2-butene (33.6 mg, 0.195 mmol), then Hoveyda-Grubbs second generation catalyst (4.7 mg, 0.0075 mmol, 5 mol %). The pressure tube was capped, and the reaction was heated to 40 $^oC$. The reaction stirred at 40 $^oC$ for 1 hour, where additional Hoveyda-Grubbs second-generation catalyst (4.7 mg,

0.0075 mmol, 5 mol %) was added. The reaction continued to stir for 5 hours (stalled progression by TLC). The reaction was concentrated under reduced pressure, and the crude mixture was purified via flash chromatography (silica, 0%–50% EtOAc in hexanes) to provide title **3.11.2** (25.2 mg, 0.0926 mmol, 62% yield, 84% based on recovered starting material) as a pale yellow oil, along with unreacted **3.9.5** (7.9 mg, 0.0395 mmol).

**FTIR** (neat): 2930, 2885, 2849, 2403, 1738, 1456, 1427, 1364, 1232, 1115, 1092, 1047, 1026, 995, 945, 916, 876, 833, 785, 733, 665, 617 $cm^{-1}$;

**Optical Rotation**: $[\alpha]_D = -124$ ($c$ = 1.07, $CHCl_3$);

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.08 (dddd, $J$ = 11.7, 6.6, 3.1, 1.9 Hz, 1H, (P)O-CH-CH=C<u>H</u>-$CH_2$-O(P)), 5.95 (dtd, $J$ = 15.6, 5.6, 1.3 Hz, 1H, -CH=C<u>H</u>-$CH_2$OAc), 5.78 (ddt, $J$ = 15.5, 5.8, 1.5 Hz, 1H, -C<u>H</u>=CH-$CH_2$OAc), 5.65 (ddd, $J$ = 11.6, 4.0, 2.6 Hz, 1H, (P)O-CH-C<u>H</u>=CH-$CH_2$-O(P)), 5.19 (dtt, $J$ = 16.0, 3.9, 1.9 Hz, 1H, (P)O-C<u>H</u>-CH=CH-$CH_2$-O(P)), 5.09 – 5.02 (m, 1H, -$CH_2$-(P)O-C<u>H</u>-CH=CH-$CH_2$OAc), 4.92 (ddq, $J$ = 14.8, 3.9, 2.6 Hz, 1H, (P)O-C<u>H</u>$_a$H$_b$-CH=CH-), 4.59 (dt, $J$ = 5.6, 1.2 Hz, 2H, -CH=CH-C<u>H</u>2-OAc), 4.44 (ddd, $J$ = 22.9, 14.8, 6.6 Hz, 1H, (P)O-CH$_a$<u>H</u>$_b$-CH=CH-), 2.48 – 2.34 (m, 1H, (P)O-CH-C<u>H</u>$_a$H$_b$-CH-O(P)), 2.09 (s, 3H, -CH=CH-$CH_2$-OC(O)(C<u>H</u>$_3$)), 1.84 (dq, $J$ = 14.6, 1.8 Hz, 1H, (P)O-CH-CH$_a$<u>H</u>$_b$-CH-O(P)), 0.95 – 0.13 (m, 3H, -$BH_3$);

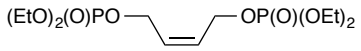
**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 170.5 (C=O), 130.6 (CH), 130.2 (d, $J_{CP}$ = 7.2 Hz, CH), 128.9 (CH), 127.7 (CH), 77.3 (d, $J_{CP}$ = 9.0 Hz, CH), 69.72 (d, $J_{CP}$ = 7.0 Hz, CH), 63.41 ($CH_2$), 63.35 ($CH_2$), 35.7 (d, $J_{CP}$ = 5.8 Hz, $CH_2$), 20.84 ($CH_3$);

**$^{31}$P NMR** (162 MHz, $CDCl_3$) δ 113.1 (short, d (br), $J$ = 151.1 Hz);

**$^{11}$B NMR** (160 MHz, $CDCl_3$) δ -42.7 (dq, *J* = 98.5, 98.5 Hz);

**HRMS** cald for oxidized parent molecule $C_{11}H_{15}O_6PNa$ $(M+Na)^+$ 297.0504; found 297.0501 (TOF MS ES+).

**(*Z*)-but-2-ene-1,4-diyl tetraethyl bis(phosphate) ($C_{12}H_{26}O_8P_2$, 3.11.7-SI)**




**3.11.7-SI**

To a solution of (Z)-but-2-ene-1,4-diol (0.50 g, 5.68 mmol) in methylene chloride (57 mL) was added triethylamine (2.4 mL, 17.0 mmol) and 4-dimethylaminopyridine (DMAP) (0.0693 g, 0.568 mmol) under argon. The reaction was cooled to 0 $^oC$ and diethylchlorophosphate (1.9 mL, 13.1 mmol) was added dropwise. The reaction was allowed to warm to room temperature in the ice bath and stirred at room temperature for 1 hour (complete by TLC). The heterogeneous mixture was concentrated under reduced pressure and immediately purified via flash chromatography (silica, 0%–50% acetone in EtOAc) to provide **3.11.7-SI** (1.47 g, 4.08 mmol, 72% yield) as a colorless liquid.

**FTIR** (neat): 2984, 2934, 2910, 1479, 1394, 1265, 1167, 1030, 982, 870, 818, 802, 754, 525 $cm^{-1}$;

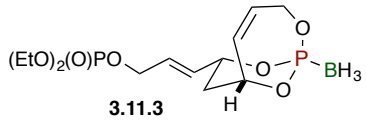
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 5.80 (t, *J* = 4.2 Hz, 2H), 4.62 (dd, *J* = 8.8, 4.3 Hz, 4H), 4.10 (p, *J* = 7.3 Hz, 8H), 1.33 (t, *J* = 7.1 Hz, 12H);

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 128.4 (d, $J_{CP}$ = 6.8 Hz, CH), 63.8 (d, $J_{CP}$ = 5.9 Hz, $CH_2$), 62.5 (d, $J_{CP}$ = 5.4 Hz, $CH_2$), 16.1 (d, *J* = 6.7 Hz, $CH_3$);

**$^{31}$P NMR** (162 MHz, $CDCl_3$) δ -0.84 (hept, $J$ = 8.5 Hz);

**HRMS** cald for $C_{12}H_{26}O_8P_2Na$ $(M+Na)^+$ 383.1001; found 383.0996 (TOF MS ES+).

**(*E*)-3-((1*S*,6*R*,8*R*)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl-1-borane)allyl diethyl phosphate ($C_{13}H_{25}BO_7P_2$, 3.11.3)**




**3.11.3**

To a solution of ($R_P$,*R*,*R*)-bicyclic phosphite-borane **3.9.5** (50.0 mg, 0.250 mmol) under argon was added dry, methylene chloride (1.9 mL, degassed via 3 freeze-degas-thaw cycles), (*Z*)-but-2-ene-1,4-diyl tetraethyl bis(phosphate) (**3.11.7-SI**, 0.180 g, 0.500 mmol), then Hoveyda-Grubbs second generation catalyst (4.7 mg, 0.0075 mmol, 3 mol %). The reaction mixture was heated to reflux and stirred at reflux for 2 hours, where additional Hoveyda-Grubbs second-generation catalyst (4.7 mg, 0.0075 mmol, 3 mol %) was added. The reaction continued to stir for 4 hours (stalled progression by TLC). The reaction was concentrated under reduced pressure, and the crude mixture was purified via flash chromatography (silica, 0%–100% EtOAc in hexanes) to provide title **3.11.3** (81.7 mg, 0.223 mmol, 89% yield) as a colorless, viscous oil in a 7:1 mixture of *E*- and *Z*-isomers. The mixture was further purified to exclusively provide the major *E*-isomer for full characterization and further use in the following cuprate addition reactions (*vide infra*).

**Yield:** 89% (dr ~ 7:1, crude $^1$H, $^{13}$C)

**FTIR** (neat): 2984, 2908, 2405, 1458, 1396, 1261, 1165, 1113, 1094, 1026, 995, 945, 914, 833, 798, 784, 733, 663, 621, 536 $cm^{-1}$;

**Optical Rotation**: $[\alpha]_D = -92.3$ ($c = 1.27$, $CHCl_3$);

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.08 (dddd, $J$ = 11.7, 6.7, 3.2, 1.9 Hz, 1H, (P)O-CH-CH=C<u>H</u>-$CH_2$-O(P)), 5.97 (dt, $J$ = 15.5, 5.3 Hz, 1H, -CH=C<u>H</u>-$CH_2OP(O)(OEt)_2$), 5.83 (ddt, $J$ = 15.4, 5.5, 1.6 Hz, 1H, -C<u>H</u>=CH-$CH_2OP(O)(OEt)_2$), 5.65 (ddd, $J$ = 11.7, 4.0, 2.6 Hz, 1H, (P)O-CH-CH=C<u>H</u>-$CH_2$-O(P)), 5.23 – 5.15 (m, 1H, (P)O-C<u>H</u>-CH=CH-$CH_2$-O(P)), 5.10 – 5.01 (m, 1H, -$CH_2$-(P)O-C<u>H</u>-CH=CH-$CH_2OP(O)(OEt)_2$), 4.91 (dp, $J$ = 14.8, 2.8 Hz, 1H, (P)O-C<u>$H_a$</u>$H_b$-CH=CH-), 4.55 (ddt, $J$ = 7.9, 5.3, 1.3 Hz, 2H, -CH=CH-C<u>$H_2$</u>-$OP(O)(OEt)_2$), 4.44 (ddd, $J$ = 22.9, 14.8, 6.7 Hz, 1H, (P)O-$CH_a$<u>$H_b$</u>-CH=CH-), 4.17 – 4.07 (m, 4H, -$OP(O)(OC$<u>$H_2$</u>$CH_3)_2$), 2.38 (ddd, $J$ = 14.7, 12.0, 6.0 Hz, 1H, (P)O-CH-C<u>$H_a$</u>$H_b$-CH-O(P)), 1.84 (dq, $J$ = 14.6, 1.7 Hz, 1H, (P)O-CH-$CH_a$<u>$H_b$</u>-CH-O(P)), 1.34 (tt, $J$ = 7.1, 1.3 Hz, 6H, -$OP(O)(OCH_2C$<u>$H_3$</u>$)_2$), 0.89 – 0.17 (m, 3H, -$BH_3$);

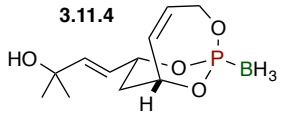
**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 130.6 (CH), 129.9 (d, $J_{CP}$ = 7.2 Hz, CH), 128.9 (CH), 127.9 (d, $J_{CP}$ = 7.2 Hz, CH), 77.3 (d, $J_{CP}$ = 8.9 Hz, CH), 69.6 (d, $J_{CP}$ = 6.9 Hz, CH), 66.2 (d, $J_{CP}$ = 5.2 Hz, $CH_2$), 63.9 (d, $J_{CP}$ = 5.9 Hz, 2 x $CH_2$), 63.4 (d, $J_{CP}$ = 8.0 Hz, $CH_2$), 35.7 (d, $J_{CP}$ = 5.8 Hz, $CH_2$), 16.1 (d, $J_{CP}$ = 6.8 Hz, 2 x $CH_3$);

**$^{31}$P NMR** (162 MHz, $CDCl_3$) δ 113.04 (short, d (br), $J$ = 154.9 Hz), -1.02 (p, $J$ = 8.4 Hz);

**$^{11}$B NMR** (160 MHz, $CDCl_3$) δ -42.8 (dq, $J$ = 98.9, 98.9 Hz);

**HRMS** cald for $C_{13}H_{25}BO_7P_2Na$ $(M+Na)^+$ 389.1066; found 389.1082 (TOF MS ES+).

**(*E*)-4-((1*S*,6*R*,8*R*)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl-1-borane)-2-methylbut-3-en-2-ol ($C_{11}H_{20}BO_4P$, 3.11.4)**




To a solution of ($R_P$,*R*,*R*)-bicyclic phosphite-borane **3.9.5** (30.0 mg, 0.150 mmol) in a pressure tube under argon was added dry, methylene chloride (1.9 mL, degassed via 3 freeze-degas-thaw cycles), 2-methyl-3-buten-2-ol (47 mL, 0.450 mmol), then Hoveyda-Grubbs second generation catalyst (2.8 mg, 0.0045 mmol, 3 mol %). The pressure tube was capped, and the reaction was heated to 40 $^oC$. The reaction stirred at 40 $^oC$ for 3 hours, where additional Hoveyda-Grubbs second-generation catalyst (2.8 mg, 0.0045 mmol, 3 mol %) was added. The reaction continued to stir for 5 hours (stalled progression by TLC). The reaction was concentrated under reduced pressure, and the crude mixture was purified via flash chromatography (silica, 0%–100% EtOAc in hexanes) to provide title **3.11.4** (19.8 mg, 0.0767 mmol, 51% yield, 77% based on recovered starting material) as a colorless, viscous oil, along with unreacted **3.9.5** (10.1 mg, 0.0505 mmol).

**FTIR** (neat): 3381 (br), 2972, 2927, 2885, 2404, 1458, 1396, 1364, 1258, 1231, 1113, 1092, 1076, 1049, 1026, 995, 947, 914, 874, 835, 813, 733, 623, 588 $cm^{-1}$;

**Optical Rotation**: $[\alpha]_D = -127$ ($c = 0.43$, $CHCl_3$);

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.08 (dddd, $J$ = 11.7, 6.6, 3.2, 1.9 Hz, 1H, (P)O-CH-CH=C<u>H</u>-$CH_2$-O(P)), 5.98 (dd, $J$ = 15.5, 1.2 Hz, 1H, -CH=C<u>H</u>-$C(CH_3)_2$-OH), 5.72 (dd, $J$

= 15.5, 6.2 Hz, 1H, -CH=CH-C(CH$_3$)$_2$-OH), 5.65 (ddd, *J* = 11.6, 4.0, 2.6 Hz, 1H, (P)O-CH-CH=CH-CH$_2$-O(P)), 5.19 (dtt, *J* = 16.0, 3.9, 2.0 Hz, 1H, (P)O-CH-CH=CH-CH$_2$-O(P)), 5.08 – 5.00 (m, 1H, CH$_2$-(P)O-CH-CH=C(CH$_3$)$_2$-OH), 4.92 (ddq, *J* = 14.8, 3.9, 2.6 Hz, 1H, (P)O-CH$_a$H$_b$-CH=CH-), 4.44 (ddd, *J* = 22.8, 14.8, 6.7 Hz, 1H, (P)O-CH$_a$H$_b$-CH=CH-), 2.41 (ddd, *J* = 14.7, 12.0, 6.0 Hz, 1H, (P)O-CH-CH$_a$H$_b$-CH-O(P)), 1.83 (dq, *J* = 14.6, 1.7 Hz, 1H, (P)O-CH-CH$_a$H$_b$-CH-O(P)), 1.59 (s (br), 1H, -OH), 1.33 (d, *J* = 6.2 Hz, 6H, -CH=CH-C(CH$_3$)$_2$-OH), 0.91 – 0.15 (m, 3H, -BH$_3$);

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 141.7 (CH), 130.8 (CH), 128.8 (CH), 123.8 (d, $J_{CP}$ = 7.3 Hz, CH), 77.4 (d, $J_{CP}$ = 8.8 Hz, CH), 70.5 (-C(CH$_3$)-OH), 70.4 (d, *J* = 6.9 Hz, CH), 63.4 (d, $J_{CP}$ = 8.0 Hz, CH$_2$), 36.0 (d, $J_{CP}$ = 5.8 Hz, CH$_2$), 29.6 (2 x CH$_3$);

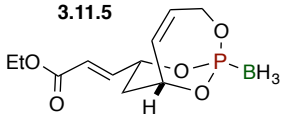
**$^{31}$P NMR** (162 MHz, $CDCl_3$) δ 112.8 (short, d (br), *J* = 138.8 Hz);

**$^{11}$B NMR** (160 MHz, $CDCl_3$) δ -42.7 (dq, *J* = 98.5, 97.8 Hz);

**HRMS** cald for phosphite fragment of parent molecule $C_{11}H_{17}O_4PNa$ $(M+Na)^+$ 267.0762; found 267.0773 (TOF MS ES+).

**(*E*)-ethyl 3-((1*S*,6*R*,8*R*)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl-1-borane)acrylate ($C_{11}H_{18}BO_5P$, 3.11.5)**

**3.11.5**




To a clean, dry round bottom flask equipped with a reflux condenser and magnetic stirbar was added (*R*$_P$,*R*,*R*)-bicyclic phosphite-borane **3.9.5** (60.0 mg, 0.300 mmol), 1,2-

dichloroethane (dry, degassed via 3 freeze-degas-thaw cycles, 6 mL), tetrafluoro-1,4-benzoquinone (5.4 mg, 0.0300 mmol), ethyl acrylate (freshly distilled over $CaH_2$ to remove hydroquinone stabilizer, 64 mL, 0.600 mmol), then Hoveyda-Grubbs second-generation catalyst (5.6 mg, 0.009 mmol, 3 mol %). The reaction was heated to reflux and stirred at reflux for 2 hours, at which point additional HG-II (5.6 mg, 0.009 mmol, 3 mol %) and ethyl acrylate (64 mL, 0.600 mmol), and the reaction continued to stir for 5 hours (stalled progression by TLC). The reaction was concentrated under reduced pressure and purified via flash chromatography (silica, 50%–70% EtOAc in Hexanes) to provide **3.11.5** (38.2 mg, 0.140 mmol, 47% yield) as a pale yellow liquid.

**FTIR** (neat): 2980, 2930, 2405, 1718, 1666, 1444, 1396, 1367, 1306, 1279, 1258, 1232, 1180, 1119, 1094, 1051, 1030, 955, 914, 887, 929, 787, 775, 754, 663, 611 $cm^{-1}$;

**Optical Rotation**: $[\alpha]_D = -85.6$ ($c = 0.85$, $CHCl_3$);

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.82 (ddd, $J$ = 15.5, 4.2, 0.7 Hz, 1H, -C<u>H</u>=CH-$CO_2CH_2CH_3$), 6.20 (dd, $J$ = 15.6, 1.9 Hz, 1H, -CH=C<u>H</u>-$CO_2CH_2CH_3$), 6.11 (dddd, $J$ = 11.7, 6.7, 3.1, 1.9 Hz, 1H, (P)O-CH-CH=C<u>H</u>-$CH_2$-O(P)), 5.67 (ddd, $J$ = 11.6, 4.0, 2.5 Hz, 1H, (P)O-CH-CH=C<u>H</u>-$CH_2$-O(P)), 5.21 (dddq, $J$ = 19.1, 12.0, 4.4, 2.0 Hz, 2H, (P)O-C<u>H</u>-CH=CH-$CH_2$-O(P), $CH_2$-(P)O-C<u>H</u>-CH=$CO_2CH_2CH_3$), 4.92 (ddq, $J$ = 14.8, 4.0, 2.6 Hz, 1H, (P)O-C<u>H</u>$_a$H$_b$-CH=CH-), 4.46 (ddd, $J$ = 23.0, 14.8, 6.6 Hz, 1H, (P)O-CH$_a$<u>H</u>$_b$-CH=CH-), 4.21 (q, $J$ = 7.1 Hz, 2H, -$CO_2$C<u>H</u>$_2$$CH_3$), 2.37 (ddd, $J$ = 14.7, 12.1, 6.0 Hz, 1H, (P)O-CH-C<u>H</u>$_a$H$_b$-CH-O(P)), 1.92 (dq, $J$ = 14.6, 1.7 Hz, 1H, (P)O-CH-CH$_a$<u>H</u>$_b$-CH-O(P)), 1.29 (t, $J$ = 7.1 Hz, 3H, -$CO_2CH_2$C<u>H</u>$_3$), 0.92 – 0.19 (m, 3H, -$BH_3$);

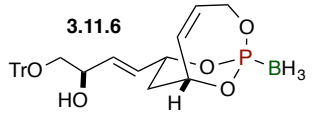
**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 165.7 (C=O), 142.7 (d, $J_{CP}$ = 7.1 Hz, CH), 130.4 (CH), 129.3 (CH), 122.7 (CH), 77.4 (d, $J_{CP}$ = 8.0 Hz, CH), 68.5 (d, $J_{CP}$ = 7.1 Hz, CH), 63.5 (d, $J_{CP}$ = 8.0 Hz, $CH_2$), 60.8 ($CH_2$), 35.2 (d, $J_{CP}$ = 5.9 Hz, $CH_2$), 14.2 ($CH_3$);

**$^{31}$P NMR** (162 MHz, $CDCl_3$) δ 113.5 (short, d (br), $J$ = 147.4 Hz);

**$^{11}$B NMR** (160 MHz, $CDCl_3$) δ -42.8 (dq, $J$ = 97.7, 97.2 Hz);

**HRMS** cald for oxidized parent molecule $C_{11}H_{15}O_6PNa$ $(M+Na)^+$ 297.0504; found 297.0503 (TOF MS ES+).

**(*R*,*E*)-4-((1*S*,6*R*,8*R*)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl-1-borane)-1-(trityloxy)but-3-en-2-ol ($C_{29}H_{32}BO_5P$, 3.11.6)**




To a solution of ($R_P$,*R*,*R*)-bicyclic phosphite-borane **3.9.5** (30.0 mg, 0.150 mmol) in a pressure tube under argon was added dry methylene chloride (1.9 mL, degassed via 3 freeze-degas-thaw cycles), (*R*)-1-(trityloxy)but-3-en-2-ol[7] (149 mg, 0.450 mmol), *p*-benzoquinone (1.6 mg, 0.015 mmol), then Hoveyda-Grubbs second generation catalyst (2.8 mg, 0.0045 mmol, 3 mol %). The pressure tube was capped, and the reaction was heated to 40 $^oC$. The reaction stirred at 40 $^oC$ for 2 hours, where additional Hoveyda-Grubbs second-generation catalyst (2.8 mg, 0.0045 mmol, 3 mol %) was added. The reaction continued to stir for 2 hours (complete by TLC). The reaction was concentrated

[7] Aragonès, S.; Bravo, F.; Díaz, Y.; Matheu, M. I.; Castillón, S. *Tetrahedron Lett.* **2003**, *44*, 3771–3773.

under reduced pressure, and the crude mixture was purified via flash chromatography (silica, 0%–70% EtOAc in hexanes) to provide title **3.11.6** (71.3 mg, 0.142 mmol, 95% yield) as a sticky, white foam. Note: **3.11.6** was isolated as a sticky, white foam that stored fairly well—when completely dry—at lower temperatures under inert atmosphere. However, extended store times (>5 months) led to decomposition even at lower temperature. Storage on the bench-top at ambient temperature led to decomposition within a few weeks and more quickly if the compound was not properly dried.

**FTIR** (neat): 3568, 3466 (br), 3057, 3018, 2926, 2873, 2405, 1489, 1448, 1396, 1259, 1219, 1117, 1092, 1076, 1047, 1028, 995, 947, 916, 879, 831, 752, 708, 633, 613, 592 $cm^{-1}$;

**Optical Rotation**: $[\alpha]_D = -61.2$ ($c$ = 1.47, $CHCl_3$);

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.47 – 7.43 (m, 6H, Aromatic C-H x 6), 7.37 – 7.32 (m, 6H, Aromatic C-H x 6), 7.31 – 7.25 (m, 3H, Aromatic C-H x 3), 6.07 (dddd, $J$ = 11.7, 6.7, 3.2, 1.9 Hz, 1H, (P)O-CH-CH=C<u>H</u>-$CH_2$-O(P)), 5.84 – 5.78 (m, 2H, -C<u>H</u>=C<u>H</u>-CH(OH)-$CH_2$OTr), 5.63 (ddd, $J$ = 11.6, 4.0, 2.5 Hz, 1H, (P)O-CH-C<u>H</u>=CH-$CH_2$-O(P)), 5.17 (dtt, $J$ = 16.0, 4.0, 1.9 Hz, 1H, (P)O-C<u>H</u>-CH=CH-$CH_2$-O(P)), 5.01 (dq, $J$ = 11.9, 2.4 Hz, 1H, -$CH_2$-(P)O-C<u>H</u>-CH=CH-CH(OH)-$CH_2$OTr), 4.96 – 4.88 (m, 1H, (P)O-C<u>H$_a$</u>H$_b$-CH=CH-), 4.43 (ddd, $J$ = 23.0, 14.8, 6.7 Hz, 1H, (P)O-C<u>H$_a$</u>H$_b$-CH=CH-), 4.34 (dq, $J$ = 6.7, 3.2 Hz, 1H, -CH=CH-C<u>H</u>(OH)-$CH_2$OTr), 3.27 (dd, $J$ = 9.5, 3.6 Hz, 1H, -CH=CH-CH(OH)-C<u>H$_a$</u>H$_b$OTr), 3.11 (dd, $J$ = 9.5, 7.8 Hz, 1H, -CH=CH-CH(OH)-CH$_a$<u>H$_b$</u>OTr), 2.55 – 2.52 (m, 1H, -CH=CH-CH(O<u>H</u>)-$CH_2$OTr), 2.37 (ddd, $J$ = 14.7, 11.9, 6.0 Hz, 1H, (P)O-

CH-C$\underline{H}_a$H$_b$-CH-O(P)), 1.82 (dq, $J$ = 14.6, 1.8 Hz, 1H, (P)O-CH-CH$_a\underline{H}_b$-CH-O(P)), 0.90 – 0.13 (m, 3H, -$BH_3$);

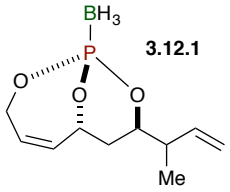
**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 143.5 (aromatic C x 3), 132.3 (CH), 130.7 (CH), 128.8 (aromatic CH x 6), 128.6 (aromatic C-H x 6), 128.5 (d, $J_{CP}$ = 7.8 Hz, CH), 127.9 (CH), 127.2 (aromatic CH x 3), 86.9 (CH), 77.4 (d, $J_{CP}$ = 8.8 Hz, CH), 70.6 (CH), 70.1 (d, $J_{CP}$ = 6.9 Hz, CH), 67.2 ($CH_2$), 63.3 (d, $J_{CP}$ = 7.9 Hz, $CH_2$), 35.83 (d, $J_{CP}$ = 5.7 Hz, $CH_2$);

**$^{31}$P NMR** (162 MHz, $CDCl_3$) δ 112.9 (short, d (br), $J$ = 144.1 Hz);

**$^{11}$B NMR** (160 MHz, $CDCl_3$) δ -42.7 (qd, $J$ = 99.5, 90.8 Hz);

**HRMS** cald for $C_{29}H_{32}BO_5PNa$ $(M+Na)^+$ 525.1978; found 525.1996 (TOF MS ES+).

**(1*R*,6*R*,8*R*)-8-(but-3-en-2-yl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene ($C_{10}H_{18}BO_3P$, 3.12.1)**



3.12.1

In a glovebox, under argon, CuCN (7.0 mg, 0.074 mmol) and LiCl (6.0 mg, 0.15 mmol) were added to a pear-shaped flask equipped with a magnetic stirbar. The flask was capped with a rubber septum, removed from the glovebox, and equipped with an argon inlet. THF (0.25 mL) was added the flask, and the mix stirred at room temperature to dissolve all solids (~25 min). The flask was cooled to an external temperature of -30$^o$C, and $Me_2Zn$ (0.07 mL, 1.0 M in hexanes) was added to the reaction mixture, drop-wise,

slowly. The mix continued to stir at -30°C for 1 hour to generate the active (dimethyl)cyanocuprate. The flask was then cooled to -40°C, where **3.11.3** (18 mg, 0.049 mmol) in THF (0.5 mL) was added, drop-wise, slowly. The reaction stirred while warming from -40°C to -20°C over 2 hours (complete by TLC). The reaction was quenched at -20°C with saturated ammonium chloride (1 mL) and stirred while warming to +10°C over 1 hour (salt and pepper solids formed and the aqueous layer turned blue). The biphasic solution was filtered over celite and separated. The aqueous layer was extracted with EtOAc (3 x 2 mL), and the organic layers were combined, dried over sodium sulfate, filtered over celite, and concentrated under reduced pressure. The crude mixture was purified via flash chromatography (silica, 0%–40% EtOAc in hexanes) to provide **3.12.1** (5.6 mg, 0.025 mmol, 50% yield) as an off-white solid and 2:1 mixture of diastereomers. Note: $^{13}C$ NMR signal designations A and B relate to signals from the major (A) and/or minor (B) diastereomers.

**Yield:** 50% (dr ~ 2:1, crude $^{1}H$)

**FTIR** (neat): 2972, 2930, 2883, 2403, 1454, 1258, 1099, 1047, 1024, 993, 953, 912, 873, 833, 791, 710, 654, 608, 584 $cm^{-1}$;

**Optical Rotation**: $[\alpha]_D = -120$ ($c = 0.26$, $CHCl_3$);

**$^{1}H$ NMR** (500 MHz, $CDCl_3$) δ 6.05 (ddtd, $J$ = 12.1, 6.8, 3.5, 1.9 Hz, 1H, (P)O-CH-CH=C<u>H</u>-$CH_2$-O(P)), 5.79 (ddd, $J$ = 17.2, 10.4, 7.7 Hz, 1H, -CH($CH_3$)-C<u>H</u>=$CH_2$), 5.65 – 5.58 (m, 1H, (P)O-CH-C<u>H</u>=CH-$CH_2$-O(P)), 5.21 – 5.06 (m, 3H, -CH($CH_3$)-CH=C<u>$H_2$</u>, (P)O-C<u>H</u>-CH=CH-$CH_2$-O(P)), 4.91 (ddq, J = 14.8, 3.9, 2.6 Hz, 1H, (P)O-C<u>$H_a$</u>$H_b$-

CH=CH-), 4.51 – 4.37 (m, 2H, (P)O-$CH_a\underline{H}_b$-CH=CH-, (P)O-C<u>H</u>-CH($CH_3$)-$CH=CH_2$), 2.47 – 2.32 (m, 2H, (P)O-CH-C<u>H</u>($CH_3$)-$CH=CH_2$, (P)O-CH-C<u>$H_a$</u>$H_b$-CH-O(P)), 1.82 (dq, J = 14.7, 1.7 Hz, 0.5 H, Minor - (P)O-CH-$CH_a\underline{H}_b$-CH-O(P)), 1.65 (dq, J = 14.6, 1.8 Hz, 1H, Major - (P)O-CH-$CH_a\underline{H}_b$-CH-O(P)), 1.12 (dd, J = 6.8, 1.5 Hz, 3H, (P)O-CH-CH(C<u>$H_3$</u>)-$CH=CH_2$), 0.86 – 0.18 (m, 3H, -$BH_3$);

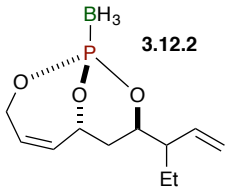
**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 138.1 ($CH^B$), 137.7 ($CH^A$), 131.1 (2 x $CH^{A,B}$), 128.7 ($CH^A$), 128.6 ($CH^B$), 116.9 ($CH^B$), 116.8 ($CH^A$), 77.7 (d, $J_{CP}$ = 8.7 Hz, $CH^B$), 77.5 (d, $J_{CP}$ = 8.7 Hz, $CH^A$), 73.6 (d, $J_{CP}$ = 7.5 Hz, $CH^B$), 73.49 (d, $J_{CP}$ = 7.6 Hz, $CH^A$), 63.3 (d, $J_{CP}$ = 8.1 Hz, 2 x $CH^{A,B}$), 43.1 (d, $J_{CP}$ = 6.2 Hz, $CH^B$), 42.2 (d, $J_{CP}$ = 6.0 Hz, $CH^A$), 33.5 (d, $J_{CP}$ = 5.7 Hz, $CH^B$), 32.6 (d, $J_{CP}$ = 5.8 Hz, $CH^A$), 15.5 ($CH_3{}^B$), 15.2 ($CH_3{}^A$);

**$^{31}$P NMR** (162 MHz, $CDCl_3$) δ 113.2 (short, broad, s);

**$^{11}$B NMR** (160 MHz, $CDCl_3$) δ -42.78 (dq, $J$ = 96.7, 95.4 Hz);

**HRMS** cald for oxidized parent molecule $C_{10}H_{15}O_4PNa$ $(M+Na)^+$ 253.0606; found 253.0606 (TOF MS ES+).

**(1*R*,6*R*,8*R*)-8-(pent-1-en-3-yl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-borane ($C_{11}H_{20}BO_3P$, 3.12.2)**




3.12.2

In a glovebox, under argon, CuCN (15.4 mg, 0.172 mmol) and LiCl (14.6 mg, 0.344 mmol) were added to a pear-shaped flask equipped with a magnetic stirbar. The flask was capped with a rubber septum, removed from the glovebox, and equipped with an argon inlet. THF (0.2 mL) was added the flask, and the mix stirred at room temperature to dissolve all solids (~25 min). The flask was cooled to an external temperature of -30°C, and $Et_2Zn$ (0.18 mL, 1.0 M in hexanes) was added to the reaction mixture, drop-wise, slowly. The mix continued to stir at -30°C for 35 minutes to generate the active (diethyl)cyanocuprate. To the stirring cuprate solution was added **3.11.3** (18 mg, 0.049 mmol) in THF (0.5 mL), drop-wise, slowly. The reaction stirred at -30°C for 2 hours (complete by TLC). The reaction was quenched at -30°C with saturated ammonium chloride (1 mL) and stirred while warming to 0°C over 1 hour (salt and pepper solids formed and the aqueous layer turned blue). The biphasic solution was filtered over celite and separated. The aqueous layer was extracted with EtOAc (3 x 2 mL), and the organic layers were combined, dried over sodium sulfate, filtered over celite, and concentrated under reduced pressure. The crude mixture was purified via flash chromatography (silica, 0%–40% EtOAc in hexanes) to provide **3.12.2** (7.6 mg, 0.031 mmol, 55% yield) as a pale

yellow oil and 2:1 mixture of diastereomers (Note: A small amount of major diastereomer (dr ~ 10:1) for full characterization.)

**Yield:** 55% (dr ~ 2:1, crude $^{1}H$, $^{13}C$)

**FTIR** (neat): 2962, 2928, 2876, 2403, 1454, 1396, 1259, 1103, 1074, 1053, 1028, 995, 955, 914, 876, 829, 797, 714, 652, 611, 584 $cm^{-1}$;

**Optical Rotation**: $[\alpha]_D = -99.0$ ($c = 0.1$, $CHCl_3$);

**$^{1}H$ NMR** (500 MHz, $CDCl_3$) δ 6.05 (dddd, $J$ = 11.7, 6.7, 3.2, 2.0 Hz, 1H, (P)O-CH-CH=C$\underline{H}$-$CH_2$-O(P)), 5.68 (ddd, $J$ = 17.2, 10.3, 9.2 Hz, 1H, -CH($CH_2CH_3$)-C$\underline{H}$=$CH_2$), 5.61 (ddd, $J$ = 11.5, 4.0, 2.6 Hz, 1H, (P)O-CH-C$\underline{H}$=CH-$CH_2$-O(P)), 5.20 (dd, $J$ = 10.4, 1.9 Hz, 1H, -CH($CH_2CH_3$)-CH=C$\underline{H}_a$$H_b$), 5.19 – 5.12 (m, 1H, (P)O-C$\underline{H}$-CH=CH-$CH_2$-O(P)), 5.08 (ddd, $J$ = 17.2, 1.9, 0.8 Hz, 1H, -CH($CH_2CH_3$)-CH=$CH_a$$\underline{H}_b$), 4.91 (dddt, $J$ = 14.7, 4.0, 3.2, 2.5 Hz, 1H, (P)O-C$\underline{H}_a$$H_b$-CH=CH-), 4.58 (dtd, $J$ = 12.1, 3.2, 2.0 Hz, 1H, (P)OC$\underline{H}$-CH($CH_2CH_3$)-CH=$CH_2$), 4.47 – 4.37 (m, 1H, (P)O-$CH_a$$\underline{H}_b$-CH=CH-), 2.45 (ddd, $J$ = 14.7, 12.1, 6.1 Hz, 1H, (P)O-CH-C$\underline{H}_a$$H_b$-CH-O(P)), 2.01 (tt, $J$ = 9.0, 3.9 Hz, 1H, -C$\underline{H}$($CH_2CH_3$)-CH=$CH_2$), 1.63 – 1.57 (m, 2H, (P)O-CH-C$\underline{H}_a$$H_b$-CH-O(P), -CH(C$\underline{H}_a$$H_b$$CH_3$)-CH=$CH_2$), 1.53 – 1.41 (m, 1H, -CH($CH_a$$\underline{H}_b$$CH_3$)-CH=$CH_2$), 0.89 (t, $J$ = 7.4 Hz, 3H, -CH($CH_2$C$\underline{H}_3$)-CH=$CH_2$), 0.83 – 0.14 (m, 3H, -$BH_3$);

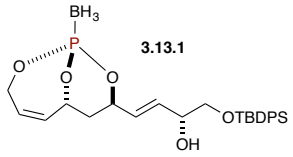
**$^{13}C$ NMR** (126 MHz, $CDCl_3$) δ 136.3 (CH), 131.1 (CH), 128.6 (CH), 118.5 ($CH_2$), 77.5 (d, $J_{CP}$ = 8.7 Hz, CH), 72.5 (d, $J_{CP}$ = 7.6 Hz, CH), 63.3 (d, $J_{CP}$ = 8.1 Hz, $CH_2$), 50.5 (d, $J_{CP}$ = 5.8 Hz, CH), 33.3 (d, $J_{CP}$ = 5.9 Hz, $CH_2$), 23.2 ($CH_2$), 11.6 ($CH_3$);

**$^{31}P$ NMR** (162 MHz, $CDCl_3$) δ 113.7 (short, broad, s);

**$^{11}$B NMR** (160 MHz, $CDCl_3$) δ -42.80 (dq, $J$ = 105.4, 101.9 Hz);

**HRMS** cald for oxidized parent molecule $C_{11}H_{17}O_4PNa$ $(M+Na)^+$ 267.0762; found 267.0764 (TOF MS ES+).

**(*R*,*E*)-4-((1*S*,6*R*,8*R*)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl-1-borane)-1-((*tert*-butyldiphenylsilyl)oxy)but-3-en-2-ol ($C_{26}H_{36}BO_5PSi$, 3.13.1)**




3.13.1

To a stirring solution of ($R_P$,*R*,*R*)-bicyclic phosphite-borane **3.9.5** (150 mg, 0.750 mmol) under argon was added dry methylene chloride (9.4 mL, degassed via 3 freeze-degas-thaw cycles), (*R*)-1-((*tert*-butyldiphenylsilyl)oxy)but-3-en-2-ol[8] (735 mg, 2.25 mmol), *p*-benzoquinone (8.1 mg, 0.075 mmol), then Hoveyda-Grubbs second generation catalyst (14.1 mg, 0.0225 mmol, 3 mol %), and the reaction was heated to reflux. The reaction stirred at reflux for 3 hours, where additional Hoveyda-Grubbs second-generation catalyst (14.1 mg, 0.0225 mmol, 3 mol %) was added. The reaction continued to stir for 3 hours (complete by TLC). The reaction was concentrated under reduced pressure, and the crude mixture was purified via flash chromatography (silica, 0%–70% EtOAc in hexanes) to provide title **3.13.1** (0.302 g, 0.607 mmol, 81% yield) as a white foam.

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[8] Williams, D. R.; Claeboe, C. D.; Liang, B.; Zorn, N.; Chow, N. S. C. *Org. Lett.* **2012**, *14*, 3866–3869.

**FTIR** (neat): 3558, 3433 (br), 3070, 2957, 2930, 2885, 2405, 1462, 1427, 1394, 1362, 1259, 1221, 1113, 1047, 1028, 995, 947, 916, 880, 824, 785, 743, 704, 613, 503, 490 $cm^{-1}$;

**Optical Rotation**: $[\alpha]_D = -51.1$ ($c$ = 1.57, $CHCl_3$);

**$^1$H NMR** (500 MHz, $CDCl_3$) 7.69 – 7.63 (m, 4H, aromatic C-H x 4), 7.48 – 7.39 (m, 6H, aromatic C-H x 6), 6.07 (dddd, $J$ = 11.7, 6.7, 3.2, 1.9 Hz, 1H, (P)O-CH-CH=C<u>H</u>-$CH_2$-O(P)), 5.86 – 5.75 (m, 2H, -C<u>H</u>=C<u>H</u>-CH(OH)-$CH_2$OTBDPS), 5.63 (ddd, $J$ = 11.6, 4.0, 2.6 Hz, 1H, (P)O-CH-C<u>H</u>=CH-$CH_2$-O(P)), 5.16 (dtt, $J$ = 15.9, 4.0, 2.0 Hz, 1H, (P)O-C<u>H</u>-CH=CH-$CH_2$-O(P)), 5.05 – 4.97 (m, 1H, -$CH_2$-(P)O-C<u>H</u>-CH=CH-CH(OH)-$CH_2$OTBDPS), 4.91 (ddq, $J$ = 14.8, 3.8, 2.6 Hz, 1H, (P)O-C<u>H</u>$_a$H$_b$-CH=CH-), 4.43 (ddd, $J$ = 22.8, 14.8, 6.7 Hz, 1H, (P)O-CH$_a$<u>H</u>$_b$-CH=CH-), 4.29 (dddd, $J$ = 6.5, 3.7, 2.4, 1.2 Hz, 1H, -CH=CH-C<u>H</u>(OH)-$CH_2$OTBDPS), 3.73 (dd, $J$ = 10.2, 3.7 Hz, 1H, -CH=CH-CH(OH)-C<u>H</u>$_a$H$_b$OTBDPS), 3.53 (dd, $J$ = 10.2, 7.4 Hz, 1H, -CH=CH-CH(OH)-CH$_a$<u>H</u>$_b$OTBDPS), 2.59 (s, 1H, -CH=CH-CH(O<u>H</u>)-$CH_2$OTBDPS), 2.35 (ddd, $J$ = 14.7, 12.0, 6.0 Hz, 1H, (P)O-CH-C<u>H</u>$_a$H$_b$-CH-O(P)), 1.80 (dq, $J$ = 14.7, 1.7 Hz, 1H, (P)O-CH-CH$_a$<u>H</u>$_b$-CH-O(P)), 1.08 (s, 9H, -OSi(Ph)$_2$-C(C<u>H</u>$_3$)$_3$), 0.52 (m, 3H, -$BH_3$);

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 135.5 (Aromatic CH x 2), 135.4 (Aromatic CH x 2) 132.8 (Aromatic C), 132.7 (Aromatic C), 132.0 (CH), 130.7 (CH), 129.93 (Aromatic CH), 129.91 (Aromatic CH), 128.8 (CH), 128.6 (d, $J_{CP}$ = 7.2 Hz, CH), 127.8 (Aromatic CH x 4), 77.4 (d, $J_{CP}$ = 8.8 Hz, CH), 71.6 (CH), 70.0 (d, $J_{CP}$ = 6.9 Hz, CH), 67.3 ($CH_2$),

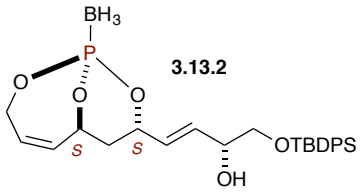
63.3 (d, $J_{CP}$ = 7.9 Hz, $CH_2$), 35.8 (d, $J_{CP}$ = 5.8 Hz, $CH_2$), 26.8 (Si-C($\underline{C}H_3)_3$), 19.2 (Si-$\underline{C}(CH_3)_3$);

**$^{31}$P NMR** (162 MHz, $CDCl_3$) δ 112.9 (short, d (br), $J$ = 147.4 Hz);

**$^{11}$B NMR** (160 MHz, $CDCl_3$) δ -42.8 (dq, $J$ = 99.8, 97.0 Hz);

**HRMS** cald for oxidized parent molecule $C_{26}H_{33}O_6PSiNa$ $(M+Na)^+$ 523.1682; found 532.1686 (TOF MS ES+).

**(*R*,*E*)-4-((1*R*,6*S*,8*S*)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl-1-borane)-1-((*tert*-butyldiphenylsilyl)oxy)but-3-en-2-ol ($C_{26}H_{36}BO_5PSi$, 3.13.2)**



3.13.2

To a stirring solution of ($S_P$,*S*,*S*)-bicyclic phosphite-borane **3.9.5** (150 mg, 0.750 mmol) under argon was added dry methylene chloride (9.4 mL, degassed via 3 freeze-degas-thaw cycles), (*R*)-1-((*tert*-butyldiphenylsilyl)oxy)but-3-en-2-ol[8] (735 mg, 2.25 mmol), *p*-benzoquinone (8.1 mg, 0.075 mmol), then Hoveyda-Grubbs second generation catalyst (14.1 mg, 0.0225 mmol, 3 mol %), and the reaction was heated to reflux. The reaction stirred at reflux for 3 hours, where additional Hoveyda-Grubbs second-generation catalyst (14.1 mg, 0.0225 mmol, 3 mol %) was added. The reaction continued to stir for 3 hours (complete by TLC). The reaction was concentrated under reduced pressure, and the

crude mixture was purified via flash chromatography (silica, 0%–70% EtOAc in hexanes) to provide title **3.13.2** (0.268 g, 0.538 mmol, 72% yield) as a white foam.

**FTIR** (neat): 3566, 3421 (br), 3070, 3013, 2940, 2858, 2405, 1460, 1427, 1394, 1362, 1259, 1113, 1047, 1028, 995, 947, 916, 878, 824, 787, 743, 704, 613, 503 $cm^{-1}$;

**Optical Rotation**: $[\alpha]_D$ = +65.2 (*c* = 1.42, $CHCl_3$);

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.68 – 7.64 (m, 4H, aromatic C-H x 4), 7.49 – 7.38 (m, 6H, aromatic C-H x 6), 6.07 (dddd, *J* = 11.7, 6.7, 3.2, 2.0 Hz, 1H, (P)O-CH-CH=C$\underline{H}$-$CH_2$-O(P)), 5.89 – 5.74 (m, 2H, -C$\underline{H}$=C$\underline{H}$-CH(OH)-$CH_2$OTBDPS), 5.63 (ddd, *J* = 11.6, 4.1, 2.6 Hz, 1H, (P)O-CH-C$\underline{H}$=CH-$CH_2$-O(P)), 5.16 (dtt, *J* = 13.8, 4.0, 2.0 Hz, 1H, (P)O-C$\underline{H}$-CH=CH-$CH_2$-O(P)), 5.01 (dqd, *J* = 10.3, 3.2, 2.2, 1.7 Hz, 1H, -$CH_2$-(P)O-C$\underline{H}$-CH=CH-CH(OH)-$CH_2$OTBDPS), 4.96 – 4.87 (m, 1H, (P)O-C$\underline{H}_a$$H_b$-CH=CH-), 4.43 (ddd, *J* = 22.8, 14.8, 6.6 Hz, 1H, (P)O-$CH_a$$\underline{H}_b$-CH=CH-), 4.28 (dtd, *J* = 7.2, 3.8, 1.2 Hz, 1H, -CH=CH-C$\underline{H}$(OH)-$CH_2$OTBDPS), 3.72 (dd, *J* = 10.2, 3.8 Hz, 1H, -CH=CH-CH(OH)-C$\underline{H}_a$$H_b$OTBDPS), 3.54 (dd, *J* = 10.2, 7.3 Hz, 1H, -CH=CH-CH(OH)-$CH_a$$\underline{H}_b$OTBDPS), 2.58 (s, 1H, -CH=CH-CH(O$\underline{H}$)-$CH_2$OTBDPS), 2.34 (ddd, *J* = 14.6, 12.0, 6.1 Hz, 1H, (P)O-CH-C$\underline{H}_a$$H_b$-CH-O(P)), 1.79 (dq, *J* = 14.6, 1.8 Hz, 1H, (P)O-CH-$CH_a$$\underline{H}_b$-CH-O(P)), 1.08 (s, 9H, -OSi$(Ph)_2$-C(C$\underline{H}_3$)$_3$), 0.86 – 0.18 (m, 3H, -$BH_3$);

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 135.52 (Aromatic CH x 2), 135.46 (Aromatic CH x 2), 132.9 (Aromatic C), 132.7 (Aromatic C), 131.9 (CH), 130.7 (CH), 129.9 (Aromatic CH x 2), 128.8 (CH), 128.4 (d, $J_{CP}$ = 7.2 Hz, CH), 127.8 (Aromatic CH x 4), 77.4 (d, $J_{CP}$ = 8.9

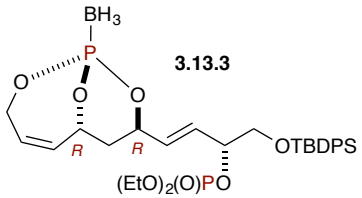
Hz, CH), 71.5 (CH), 69.9 (d, $J_{CP}$ = 6.9 Hz, CH), 67.3 ($CH_2$), 63.3 (d, $J_{CP}$ = 8.0 Hz, $CH_2$), 35.8 (d, $J_{CP}$ = 5.8 Hz, $CH_2$), 26.8 (Si-C($\underline{C}H_3)_3$), 19.2 (Si-$\underline{C}(CH_3)_3$);

**$^{31}$P NMR** (162 MHz, $CDCl_3$) δ 113.0 (short, d (br), $J$ = 147.8 Hz);

**$^{11}$B NMR** (160 MHz, $CDCl_3$) δ -42.8 (dq, $J$ = 99.1, 96.7 Hz);

**HRMS** cald for oxidized parent molecule $C_{26}H_{33}O_6PSiNa$ $(M+Na)^+$ 523.1682; found 532.1675 (TOF MS ES+).

**(*R*,*E*)-4-((1*S*,6*R*,8*R*)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl-1-borane)-1-((*tert*-butyldiphenylsilyl)oxy)but-3-en-2-yl diethyl phosphate ($C_{30}H_{45}BO_8P_2Si$, 3.13.3)**




3.13.3

To a solution of **3.13.1** (17 mg, 0.034 mmol) in methylene chloride (dry, degassed, 0.4 mL) was added *N*,*N*-diisopropyl(ethyl)amine (12 mL, 0.068 mmol) under argon, and the reaction flask was cooled to an external temperature of -30°C where diethylchlorophosphite (6 mL, 0.038 mmol) was added. The reaction was allowed to warm to 0 °C over 30 minutes (complete conversion by TLC), where tBuOOH (7.4 mL, 5-6 M in decanes) was added. The reaction was allowed to warm to RT and continued to stir at room temperature for 2 hours (complete by TLC). Excess peroxide was quenched with solid sodium sulfite, and the heterogeneous mix stirred for 20 minutes to ensure a complete quench. The reaction was filtered over cotton, concentrated under reduced

pressure, and purified via flash chromatography (silica, 0%–80% EtOAc in hexanes) to provide **3.13.3** (19.0 mg, 0.030 mmol, 88% yield) as a pale yellow, viscous oil.

**FTIR** (neat): 2957, 2930, 2895, 2405, 1462, 1427, 1261, 1113, 1028, 995, 951, 916, 879, 824, 789, 743, 704, 613, 505 $cm^{-1}$;

**Optical Rotation**: $[\alpha]_D = -55.5$ ($c = 0.29$, $CHCl_3$);

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.66 (dq, $J$ = 6.5, 1.7 Hz, 4H, aromatic C-H x 4), 7.50 – 7.36 (m, 6H, aromatic C-H x 6), 6.09 (dddd, $J$ = 11.7, 6.7, 3.1, 1.9 Hz, 1H, (P)O-CH-CH=C<u>H</u>-$CH_2$-O(P)), 5.91 (ddd, $J$ = 15.5, 6.0, 1.0 Hz, 1H, -CH=C<u>H</u>-CH(O(PO(OEt)$_2$))-$CH_2$OTBDPS), 5.85 (dd, $J$ = 15.6, 5.0 Hz, 1H, -C<u>H</u>=CH-CH(O(PO(OEt)$_2$))-$CH_2$OTBDPS), 5.63 (ddd, $J$ = 11.5, 4.0, 2.5 Hz, 1H, (P)O-CH-C<u>H</u>=CH-$CH_2$-O(P)), 5.16 (dtt, $J$ = 16.0, 3.9, 1.9 Hz, 1H, (P)O-C<u>H</u>-CH=CH-$CH_2$-O(P)), 5.03 (dp, $J$ = 11.3, 2.2 Hz, 1H, -$CH_2$-(P)O-C<u>H</u>-CH=CH-CH(O(PO(OEt)$_2$))-$CH_2$OTBDPS), 4.96 – 4.84 (m, 2H, (P)O-C<u>H</u>$_a$H$_b$-CH=CH-, -CH=CH-C<u>H</u>(O(PO(OEt)$_2$))-$CH_2$OTBDPS), 4.45 (ddd, $J$ = 22.8, 14.8, 6.6 Hz, 1H, (P)O-CH$_a$<u>H</u>$_b$-CH=CH-), 4.15 – 4.02 (m, 4H, -P(O)(O<u>C</u>$H_2$$CH_3$)$_2$), 3.81 (dd, $J$ = 10.8, 5.7 Hz, 1H, -C<u>H</u>$_a$H$_b$OTBDPS), 3.72 (ddd, $J$ = 10.7, 5.2, 1.4 Hz, 1H, -CH$_a$<u>H</u>$_b$OTBDPS), 2.32 (ddd, $J$ = 14.7, 12.0, 6.0 Hz, 1H, (P)O-CH-C<u>H</u>$_a$H$_b$-CH-O(P)), 1.79 (dq, $J$ = 14.6, 1.7 Hz, 1H, (P)O-CH-CH$_a$<u>H</u>$_b$-CH-O(P)), 1.29 (dtd, $J$ = 9.1, 7.1, 1.1 Hz, 6H, -P(O)(OCH$_2$<u>C</u>H$_3$)$_2$), 1.06 (s, 9H, -OSi(Ph)$_2$-C(C<u>H</u>$_3$)$_3$), 0.53 (d, $J$ = 122.6 Hz, 3H, -$BH_3$);

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 135.6 (Aromatic CH x 2), 135.5 (Aromatic CH x 2), 133.0 (Aromatic C), 132.9 (Aromatic C), 130.72 (d, $J_{CP}$ = 7.2 Hz, CH), 130.65 (CH), 129.84 (Aromatic CH), 129.81 (Aromatic CH), 129.3 (d, $J_{CP}$ = 3.4 Hz, CH), 128.9 (CH),

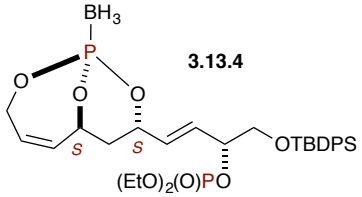
127.76 (Aromatic CH x 2), 127.75 (Aromatic CH x 2), 77.9 (d, $J_{CP}$ = 5.7 Hz, CH), 77.4 (d, $J_{CP}$ = 9.6 Hz, CH), 69.5 (d, $J_{CP}$ = 7.0 Hz, CH), 65.9 (d, $J_{CP}$ = 7.2 Hz, $CH_2$), 63.84 (d, $J_{CP}$ = 5.5 Hz, P(O)(O$\underline{C}H_2CH_3$)), 63.77 (d, $J_{CP}$ = 5.5 Hz, P(O)(O$\underline{C}H_2CH_3$)), 63.4 (d, $J_{CP}$ = 8.0 Hz, $CH_2$), 35.6 (d, $J_{CP}$ = 5.8 Hz, $CH_2$), 26.7 (Si-C($\underline{C}H_3)_3$), 19.2 (Si-$\underline{C}(CH_3)_3$), 16.1 (d, $J_{CP}$ = 2.3 Hz, P(O)(OCH$_2\underline{C}H_3$)), 16.1 (d, $J_{CP}$ = 2.5 Hz, P(O)(OCH$_2\underline{C}H_3$));

**$^{31}$P NMR** (162 MHz, $CDCl_3$) δ 113.2 (short, d (br), $J$ = 172.9 Hz), -1.81 (q, $J$ = 7.8 Hz);

**$^{11}$B NMR** (160 MHz, $CDCl_3$) δ -42.8 (dq, $J$ = 91.6, 90.1 Hz);

**HRMS** cald for phosphite fragment of parent molecule $C_{30}H_{42}O_8P_2SiNa$ $(M+Na)^+$ 643.2022; found 643.2016 (TOF MS ES+).

**(*R*,*E*)-4-((1*R*,6*S*,8*S*)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl-1-borane)-1-((*tert*-butyldiphenylsilyl)oxy)but-3-en-2-yl diethyl phosphate ($C_{30}H_{45}BO_8P_2Si$, 3.13.4)**




To a solution of **3.13.2** (77 mg, 0.155 mmol) in methylene chloride (dry, degassed, 1.5 mL) was added *N*,*N*-diisopropyl(ethyl)amine (65 mL, 0.372 mmol) under argon, and the reaction flask was cooled to an external temperature of -30$^o$C where diethylchlorophosphite (27 mL, 0.186 mmol) was added. The reaction was allowed to warm to 0 $^o$C over 30 minutes (complete conversion by TLC), where tBuOOH (37 mL, 5-6 M in decanes) was added. The reaction was allowed to warm to RT and continued to

stir at room temperature for 2 hours (complete by TLC). Excess peroxide was quenched with solid sodium sulfite, and the heterogeneous mix stirred for 30 minutes to ensure a complete quench. The reaction was filtered over cotton, concentrated under reduced pressure, and purified via flash chromatography (silica, 0%–80% EtOAc in hexanes) to provide **3.13.4** (80.7 mg, 0.127 mmol, 82% yield) as a pale yellow, viscous oil.

**FTIR** (neat): 2980, 2957, 2930, 2405, 1472, 1427, 1393, 1362, 1263, 1113, 1028, 995, 952, 916, 879, 822, 788, 741, 704, 613, 505 $cm^{-1}$;

**Optical Rotation**: $[\alpha]_D$ = +48.7 (*c* = 0.59, $CHCl_3$);

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.66 (dt, *J* = 8.1, 1.7 Hz, 4H, aromatic C-H x 4), 7.49 – 7.36 (m, 6H, aromatic C-H x 6), 6.08 (dddd, *J* = 9.6, 6.6, 3.1, 2.0 Hz, 1H, (P)O-CH-CH=C<u>H</u>-$CH_2$-O(P)), 5.91 (dd, *J* = 15.7, 5.9 Hz, 1H, -CH=C<u>H</u>-CH(O(PO(OEt)$_2$))-$CH_2$OTBDPS), 5.85 (dd, *J* = 15.6, 4.8 Hz, 1H, -C<u>H</u>=CH-CH(O(PO(OEt)$_2$))-$CH_2$OTBDPS), 5.63 (ddd, *J* = 11.6, 4.0, 2.6 Hz, 1H, (P)O-CH-C<u>H</u>=CH-$CH_2$-O(P)), 5.17 (dtd, *J* = 17.3, 4.0, 1.9 Hz, 1H, (P)O-C<u>H</u>-CH=CH-$CH_2$-O(P)), 5.02 (ddd, *J* = 14.2, 4.8, 2.2 Hz, 1H, -$CH_2$-(P)O-C<u>H</u>-CH=CH-CH(O(PO(OEt)$_2$))-$CH_2$OTBDPS), 4.96 – 4.85 (m, 2H, -(P)O-C<u>H</u>$_a$H$_b$-CH=CH-, -CH=CH-C<u>H</u>(O(PO(OEt)$_2$))-$CH_2$OTBDPS), 4.45 (ddd, *J* = 22.8, 14.8, 6.7 Hz, 1H, (P)O-CH$_a$<u>H</u>$_b$-CH=CH-), 4.17 – 4.00 (m, 4H, -P(O)(O<u>C</u>H$_2$CH$_3$)$_2$), 3.82 (dd, *J* = 10.7, 5.8 Hz, 1H, -C<u>H</u>$_a$H$_b$OTBDPS), 3.70 (ddd, *J* = 10.7, 5.2, 1.4 Hz, 1H, -CH$_a$<u>H</u>$_b$OTBDPS), 2.33 (ddd, *J* = 14.6, 12.0, 6.0 Hz, 1H, (P)O-CH-C<u>H</u>$_a$H$_b$-CH-O(P)), 1.79 (dq, *J* = 14.6, 1.8 Hz, 1H, (P)O-CH-CH$_a$<u>H</u>$_b$-CH-O(P)), 1.30 (dtd, *J* = 15.5, 7.1, 1.0 Hz,

6H, -P(O)(OCH$_2$CH$_3$)$_2$), 1.06 (s, 9H, -OSi(Ph)$_2$-C(CH$_3$)$_3$), 0.54 (d, $J$ = 133.8 Hz, 3H, -BH$_3$);

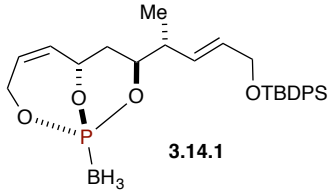
**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 135.57 (Aromatic CH x 2), 135.53 (Aromatic CH x 2), 132.97 (Aromatic C), 132.93 (Aromatic C), 130.7 (CH), 130.5 (d, $J_{CP}$ = 7.2 Hz, CH), 129.83 (Aromatic CH), 129.81 (Aromatic CH), 129.2 (d, $J_{CP}$ = 3.5 Hz, CH), 128.9 (CH), 127.75 (Aromatic CH x 2), 127.74 (Aromatic CH x 2), 77.7 (d, $J_{CP}$ = 5.5 Hz, CH), 77.3 (d, $J_{CP}$ = 9.3 Hz, CH), 69.5 (d, $J_{CP}$ = 7.0 Hz, CH), 65.9 (d, $J_{CP}$ = 7.1 Hz, CH$_2$), 63.83 (d, $J_{CP}$ = 5.5 Hz, P(O)(OCH$_2$CH$_3$)), 63.79 (d, $J_{CP}$ = 5.6 Hz, P(O)(OCH$_2$CH$_3$)), 63.4 (d, $J_{CP}$ = 8.0 Hz, CH$_2$), 35.7 (d, $J_{CP}$ = 5.8 Hz, CH$_2$), 26.7 (Si-C(CH$_3$)$_3$), 19.2 (Si-C(CH$_3$)$_3$), 16.13 (d, $J_{CP}$ = 7.4 Hz, P(O)(OCH$_2$CH$_3$)), 16.07 (d, $J_{CP}$ = 7.5 Hz, P(O)(OCH$_2$CH$_3$));

**$^{31}$P NMR** (162 MHz, $CDCl_3$) δ 113.1 (short, d (br), $J$ = 125.9 Hz), -1.77 (q, $J$ = 7.8 Hz);

**$^{11}$B NMR** (160 MHz, $CDCl_3$) δ -42.8 (dq, $J$ = 94.0, 92.4 Hz);

**HRMS** cald for $C_{30}H_{45}BO_8P_2SiNa$ $(M+Na)^+$ 657.2350; found 643.2344 (TOF MS ES+).

**(1*R*,6*S*,8*S*)-8-((*R*,*E*)-5-((*tert*-butyldiphenylsilyl)oxy)pent-3-en-2-yl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-borane ($C_{27}H_{38}BO_4PSi$, 3.14.1)**




3.14.1

In a glovebox, under argon, CuCN (12.0 mg, 0.137 mmol) and LiCl (12.0 mg, 0.274 mmol) were added to a pear-shaped flask equipped with a magnetic stirbar. The flask was

capped with a rubber septum, removed from the glovebox, and equipped with an argon inlet. THF (0.27 mL) was added the flask, and the mix stirred at room temperature to dissolve all solids (~25 min). The flask was cooled to an external temperature of -30°C, and $Me_2Zn$ (0.14 mL, 1.0 M in hexanes) was added to the reaction mixture, drop-wise, slowly. The mix continued to stir at -30°C for 1 hour to generate the active (dimethyl)cyanocuprate. The flask was then cooled to -40°C, where **3.13.2** (29.0 mg, 0.046 mmol) in THF (0.46 mL) was added, drop-wise, slowly. The reaction stirred while warming from -40°C to -10°C over 1 hour (complete by TLC). The reaction was quenched at -10°C with saturated ammonium chloride (1 mL) and stirred while warming to +10°C over 1 hour (salt and pepper solids formed and the aqueous layer turned blue). The biphasic solution was filtered over celite and separated. The aqueous layer was extracted with EtOAc (3 x 2 mL), and the organic layers were combined, dried over sodium sulfate, filtered over celite, and concentrated under reduced pressure. The crude mixture was purified via flash chromatography (silica, 0%–40% EtOAc in hexanes) to provide **3.14.1** (18.3 mg, 0.0369 mmol, 81% yield) as a colorless, viscous oil.

**FTIR** (neat): 3070, 2961, 2930, 2857, 2405, 1472, 1460, 1427, 1381, 1360, 1259, 1111, 1047, 1024, 995, 986, 957, 912, 874, 824, 785, 704, 663, 611, 505 $cm^{-1}$;

**Optical Rotation**: $[\alpha]_D$ = +60.4 (*c* = 0.75, $CHCl_3$);

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.69 (dq, *J* = 6.6, 1.7 Hz, 4H, Aromatic C-H x 4), 7.49 – 7.35 (m, 6H, Aromatic C-H x 6), 6.04 (dddd, *J* = 11.7, 6.7, 3.2, 1.9 Hz, 1H, (P)O-CH-CH=C<u>H</u>-$CH_2$-O(P)), 5.65 – 5.60 (m, 2H, -CH($CH_3$)-C<u>H</u>=C<u>H</u>-$CH_2$-OTBDPS), 5.58 (ddd,

*J* = 11.6, 4.0, 2.6 Hz, 1H, (P)O-CH-C<u>H</u>=CH-$CH_2$-O(P)), 5.13 (dtt, *J* = 15.9, 3.9, 1.9 Hz, 1H, (P)O-C<u>H</u>-CH=CH-$CH_2$-O(P)), 4.91 (ddq, *J* = 14.7, 3.9, 2.6 Hz, 1H, (P)O-C<u>H</u>$_a$H$_b$-CH=CH-), 4.50 – 4.35 (m, 2H, -(P)O-$CH_a$<u>H</u>$_b$-CH=CH-, -$CH_2$-(P)OC<u>H</u>-CH($CH_3$)-CH=CH-$CH_2$-OTBDPS), 4.25 – 4.17 (m, 2H, -CH=CH-C<u>H</u>$_2$-OTBDPS), 2.45 – 2.36 (m, 1H, -C<u>H</u>($CH_3$)-CH=CH-$CH_2$-OTBDPS), 2.27 (ddd, *J* = 14.7, 12.1, 6.1 Hz, 1H, (P)O-CH-C<u>H</u>$_a$H$_b$-CH-O(P)), 1.55 (dq, *J* = 14.6, 1.8 Hz, 1H, (P)O-CH-$CH_a$<u>H</u>$_b$-CH-O(P)), 1.09 (d, *J* = 7.1 Hz, 3H, -CH(C<u>H</u>$_3$)-CH=CH-$CH_2$-OTBDPS), 1.07 (s, 9H, -OSi(Ph)$_2$-C(C<u>H</u>$_3$)$_3$), 0.89 – 0.14 (m, 3H, -$BH_3$);

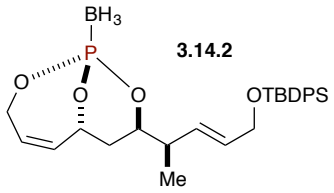
**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 135.53 (2 x aromatic CH), 135.52 (2 x aromatic CH), 133.71 (aromatic C), 133.67 (aromatic C), 131.2 (CH), 131.1 (CH), 129.64 (2 x aromatic CH), 129.59 (CH), 128.6 (CH), 127.64 (2 x aromatic CH), 127.63 (2 x CH), 77.5 (d, $J_{CP}$ = 8.7 Hz, CH), 73.6 (d, $J_{CP}$ = 7.6 Hz, CH), 64.2 ($CH_2$), 63.3 (d, $J_{CP}$ = 8.0 Hz, $CH_2$), 40.8 (d, $J_{CP}$ = 6.0 Hz, CH), 32.5 (d, $J_{CP}$ = 5.8 Hz, $CH_2$), 26.8 (Si-C(<u>C</u>H$_3$)$_3$), 19.2 (Si-<u>C</u>(CH$_3$)$_3$), 15.4 ($CH_3$);

**$^{31}$P NMR** (162 MHz, $CDCl_3$) δ 113.4 (short, broad, s);

**$^{11}$B NMR** (160 MHz, $CDCl_3$) δ -42.4 (dq, *J* = 97.3, 95.6 Hz);

**HRMS** cald for oxidized parent molecule $C_{27}H_{35}O_5PSiNa$ $(M+Na)^+$ 521.1889; found 521.1899 (TOF MS ES+).

**(1*S*,6*R*,8*R*)-8-((*R*,*E*)-5-((*tert*-butyldiphenylsilyl)oxy)pent-3-en-2-yl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-borane ($C_{27}H_{38}BO_4PSi$, 3.14.2)**




3.14.2

In a glovebox, under argon, CuCN (85.0 mg, 0.946 mmol) and LiCl (80.0 mg, 1.89 mmol) were added to a pear-shaped flask equipped with a magnetic stirbar. The flask was capped with a rubber septum, removed from the glovebox, and equipped with an argon inlet. THF (1.9 mL) was added the flask, and the mix stirred at room temperature to dissolve all solids (~25 min). The flask was cooled to an external temperature of -30$^{o}$C, and $Me_2Zn$ (0.95 mL, 1.0 M in hexanes) was added to the reaction mixture, drop-wise, slowly. The mix continued to stir at -30$^{o}$C for 1 hour to generate the active (dimethyl)cyanocuprate. The flask was then cooled to -40$^{o}$C, where **3.13.1** (150 mg, 0.236 mmol) in THF (2.4 mL) was added, drop-wise, slowly. The reaction stirred while warming from -40$^{o}$C to 0$^{o}$C over 1 hour (complete by TLC). The reaction was quenched at 0$^{o}$C with saturated ammonium chloride (2 mL) and stirred while warming to +10$^{o}$C over 1 hour (salt and pepper solids formed and the aqueous layer turned blue). The biphasic solution was filtered over celite and separated. The aqueous layer was extracted with EtOAc (3 x 2 mL), and the organic layers were combined, dried over sodium sulfate, filtered over celite, and concentrated under reduced pressure. The crude mixture was

purified via flash chromatography (silica, 0%–40% EtOAc in hexanes) to provide **3.14.2** (64.3 mg, 0.140 mmol, 59% yield) as a colorless, viscous oil.

**FTIR** (neat): 3070, 2961, 2930, 2885, 2405, 1470, 1462, 1427, 1261, 1111, 1095, 1074, 1024, 9995, 957, 912, 872, 825, 739, 704, 611, 505 $cm^{-1}$;

**Optical Rotation**: $[\alpha]_D = -69.2$ ($c = 0.24$, $CHCl_3$);

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.67 (dq, $J$ = 6.8, 1.4 Hz, 4H, aromatic C-H x 4), 7.49 – 7.32 (m, 6H, aromatic C-H x 6), 6.04 (dddd, $J$ = 11.7, 6.7, 3.2, 2.0 Hz, 1H, (P)O-CH-CH=C<u>H</u>-$CH_2$-O(P)), 5.64 (dtd, $J$ = 15.4, 4.9, 0.9 Hz, 1H, -CH($CH_3$)-CH=C<u>H</u>-$CH_2$-OTBDPS), 5.55 (ddd, $J$ = 11.6, 4.0, 2.6 Hz, 1H, (P)O-CH-C<u>H</u>=CH-$CH_2$-O(P)), 5.48 (ddt, $J$ = 15.4, 8.3, 1.6 Hz, 1H, -CH($CH_3$)-C<u>H</u>=CH-$CH_2$-OTBDPS), 5.11 (dtt, $J$ = 15.7, 3.9, 1.9 Hz, 1H, (P)O-C<u>H</u>-CH=CH-$CH_2$-O(P)), 4.90 (ddq, $J$ = 14.7, 3.9, 2.7 Hz, 1H, (P)O-C<u>H$_a$H$_b$</u>-CH=CH-), 4.42 (ddd, $J$ = 22.7, 14.8, 6.7 Hz, 1H, -(P)O-CH$_a$<u>H$_b$</u>-CH=CH-), 4.31 – 4.21 (m, 1H, -$CH_2$-(P)OC<u>H</u>-CH($CH_3$)-CH=CH-$CH_2$-OTBDPS), 4.21 – 4.15 (m, 2H, -CH=CH-C<u>H$_2$</u>-OTBDPS), 2.40 (ddd, $J$ = 14.6, 14.6, 7.1 Hz, 1H, -C<u>H</u>($CH_3$)-CH=CH-$CH_2$-OTBDPS), 2.17 (ddd, $J$ = 14.7, 12.0, 6.1 Hz, 1H, (P)O-CH-C<u>H$_a$H$_b$</u>-CH-O(P)), 1.72 (dq, $J$ = 14.6, 1.8 Hz, 1H, (P)O-CH-CH$_a$<u>H$_b$</u>-CH-O(P)), 1.08 (d, $J$ = 6.7 Hz, 3H, -CH(C<u>H$_3$</u>)-CH=CH-$CH_2$-OTBDPS), 1.06 (s, 9H, -OSi(Ph)$_2$-C(C<u>H$_3$</u>)$_3$), 0.91 – 0.16 (m, 3H, -$BH_3$);

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 135.5 (Aromatic CH x 4), 133.7 (Aromatic C), 133.6 (Aromatic C), 131.3 (CH), 131.0 (CH), 130.0 (CH), 129.69 (Aromatic CH), 129.67 (Aromatic CH), 128.6 (CH), 127.6 (Aromatic CH x 4), 77.7 (d, $J_{CP}$ = 8.8 Hz, CH), 73.8

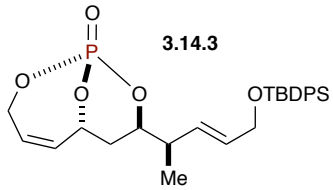
(d, $J_{CP}$ = 7.6 Hz, CH), 64.2 ($CH_2$), 63.3 (d, $J_{CP}$ = 8.1 Hz, $CH_2$), 41.7 (d, $J_{CP}$ = 6.3 Hz, CH), 33.6 (d, $J_{CP}$ = 5.9 Hz, $CH_2$), 26.8 (Si-C($\underline{C}H_3)_3$), 19.2 (Si-$\underline{C}(CH_3)_3$), 15.9 ($CH_3$);

**$^{31}$P NMR** (162 MHz, $CDCl_3$) δ 113.2 (short, broad, s);

**$^{11}$B NMR** (160 MHz, $CDCl_3$) δ -42.8 (dq, $J$ = 97.6, 84.4 Hz);

**HRMS** cald for oxidized parent molecule $C_{27}H_{35}O_5PSiNa$ $(M+Na)^+$ 521.1889; found 521.1874 (TOF MS ES+).

**(1*S*,6*R*,8*R*)-8-((*R*,*E*)-5-((*tert*-butyldiphenylsilyl)oxy)pent-3-en-2-yl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-oxide ($C_{27}H_{35}O_5PSi$, 3.14.3)**




3.14.3

To **3.14.2** (64.0 mg, 0.129 mmol) in a round bottom flask equipped with a reflux condenser and magnetic stirbar, under argon, was added dry, degassed toluene (1.6 mL) and 1,4-diazabicyclo[2.2.2]octane [DABCO] (15.0 mg, 0.129 mmol). The reaction was heated to 60 $^{o}$C and stirred for 2 hours (phosphite formation was complete by TLC). The reaction was cooled to room temperature, where tBuOOH (26 mL, 5-6 M in decanes) was added in one portion via automatic micropipette and the reaction stirred at room temperature open to air for 1 hour (complete by TLC, The reaction was subsequently quenched with solid sodium sulfite, allowed to stir at room temperature to ensure consumption of excess peroxide, filtered over celite, and concentrated under reduced

pressure. The crude mix was purified via flash chromatography (silica, 0%–100% EtOAc in hexanes) to provide the corresponding bicyclic phosphate **3.14.3** (63.5 mg, 0.127 mmol, 99% yield) as a colorless, viscous oil.

**FTIR** (neat): 3070, 2961, 2930, 2856, 1462, 1427, 1302, 1261, 1111, 1078, 976, 922, 879, 824, 743, 704, 609, 505 $cm^{-1}$;

**Optical Rotation**: $[\alpha]_D = -45.8$ ($c = 0.53$, $CHCl_3$);

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.73 – 7.63 (m, 4H, Aromatic C-H x 4), 7.52 – 7.35 (m, 6H, Aromatic C-H x 6), 6.02 (dddd, $J$ = 12.0, 6.8, 3.1, 2.1 Hz, 1H, (P)O-CH-CH=C<u>H</u>-$CH_2$-O(P)), 5.65 (dtd, $J$ = 15.4, 4.9, 0.9 Hz, 1H, -CH($CH_3$)-CH=C<u>H</u>-$CH_2$-OTBDPS), 5.57 – 5.44 (m, 2H, -CH($CH_3$)-C<u>H</u>=CH-$CH_2$-OTBDPS, (P)O-CH-C<u>H</u>=CH-$CH_2$-O(P)), 5.15 (dddd, $J$ = 24.6, 6.3, 4.3, 2.0 Hz, 1H, (P)O-C<u>H</u>-CH=CH-$CH_2$-O(P)), 5.00 (ddq, $J$ = 14.9, 5.6, 2.7 Hz, 1H, (P)O-C<u>H</u>$_a$H$_b$-CH=CH-), 4.42 – 4.33 (m, 1H, (P)O-CH$_a$<u>H</u>$_b$-CH=CH-), 4.32 – 4.27 (m, 1H, -$CH_2$-(P)OC<u>H</u>-CH($CH_3$)-CH=CH-$CH_2$-OTBDPS), 4.19 (ddd, $J$ = 5.3, 3.8, 1.6 Hz, 2H, -CH=CH-C<u>H</u>$_2$-OTBDPS), 2.44 (h, $J$ = 7.2 Hz, 1H, -C<u>H</u>($CH_3$)-CH=CH-$CH_2$-OTBDPS), 2.13 – 1.99 (m, 1H, (P)O-CH-C<u>H</u>$_a$H$_b$-CH-O(P)), 1.75 – 1.66 (m, 1H, (P)O-CH-CH$_a$<u>H</u>$_b$-CH-O(P)), 1.10 (d, $J$ = 6.7 Hz, 3H, -CH(C<u>H</u>$_3$)-CH=CH-$CH_2$-OTBDPS), 1.06 (s, 9H, -OSi(Ph)$_2$-C(C<u>H</u>$_3$)$_3$);

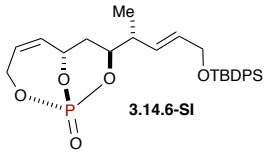
**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 135.49 (2 x aromatic CH), 135.49 (2 x aromatic CH), 133.66 (aromatic C), 133.59 (aromatic C), 131.2 (CH), 130.2 (CH), 129.9 (CH), 129.69 (CH), 129.67 (CH), 127.9 (CH), 127.63 (4 x aromatic CH), 79.8 (d, $J_{CP}$ = 7.3 Hz, CH),

77.2 (d, $J_{CP}$ = 7.2 Hz, CH), 64.2 ($CH_2$), 63.0 (d, $J_{CP}$ = 6.4 Hz, $CH_2$), 41.9 (d, $J_{CP}$ = 9.3 Hz, CH), 32.8 (d, $J_{CP}$ = 5.6 Hz, $CH_2$), 26.8 (Si-C($\underline{C}H_3)_3$), 19.2 (Si-$\underline{C}(CH_3)_3$), 15.9 ($CH_3$);

**$^{31}$P NMR** (162 MHz, $CDCl_3$) δ -3.66 (td, $J$ = 26.8, 25.1, 5.5 Hz);

**HRMS** cald for $C_{27}H_{35}O_5PSiNa$ $(M+Na)^+$ 521.1889; found 521.1888 (TOF MS ES+).

**(1*R*,6*S*,8*S*)-8-((*R*,*E*)-5-((*tert*-butyldiphenylsilyl)oxy)pent-3-en-2-yl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-oxide ($C_{27}H_{35}O_5PSi$, 3.14.6-SI)**




To **3.14.1** (54.0 mg, 0.109 mmol) in a round bottom flask equipped with a reflux condenser and magnetic stirbar, under argon, was added dry, degassed toluene (1.4 mL) and 1,4-diazabicyclo[2.2.2]octane [DABCO] (13.0 mg, 0.109 mmol). The reaction was heated to 60 $^{o}$C and stirred for 2 hours (phosphite formation was complete by TLC). The reaction was cooled to room temperature, where tBuOOH (22 mL, 5-6M in decanes) was added in one portion via automatic micropipette and the reaction stirred at room temperature open to air for 1 hour (complete by TLC, The reaction was subsequently quenched with solid sodium sulfite, allowed to stir at room temperature to ensure consumption of excess peroxide, filtered over celite, and concentrated under reduced pressure. The crude mix was purified via flash chromatography (silica, 0%–100% EtOAc in hexanes) to provide the corresponding bicyclic phosphate **3.14.6-SI** (53.3 mg, 0.106 mmol, 98% yield) as a colorless, viscous oil.

**FTIR** (neat): 3069, 3045, 2961, 2930, 2856, 2889, 1470, 1427, 1302, 1259, 1102, 1070, 986, 974, 918, 879, 824, 771, 742, 704, 609, 505 $cm^{-1}$;

**Optical Rotation**: $[\alpha]_D$ = +36.3 (*c* = 0.14, $CHCl_3$);

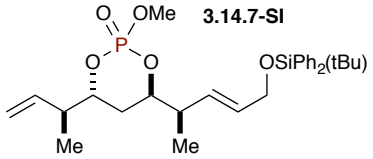
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.73 – 7.63 (m, 4H, Aromatic C-H x 4), 7.47 – 7.36 (m, 6H, Aromatic C-H x 6), 6.03 (dddd, *J* = 11.9, 6.7, 3.2, 2.1 Hz, 1H, (P)O-CH-CH=C<u>H</u>-$CH_2$-O(P)), 5.62 (dd, *J* = 4.7, 2.9 Hz, 2H, -CH($CH_3$)-C<u>H</u>=C<u>H</u>-$CH_2$-OTBDPS), 5.55 (ddd, *J* = 11.8, 3.9, 2.5 Hz, 1H, (P)O-CH-C<u>H</u>=CH-$CH_2$-O(P)), 5.16 (dddd, *J* = 24.4, 6.2, 4.0, 1.8 Hz, 1H, (P)O-C<u>H</u>-CH=CH-$CH_2$-O(P)), 5.00 (ddq, *J* = 14.8, 5.6, 2.7 Hz, 1H, (P)O-C<u>H$_a$</u>$H_b$-CH=CH-), 4.48 (ddt, *J* = 12.1, 3.8, 1.7 Hz, 1H, -$CH_2$-(P)OC<u>H</u>-CH($CH_3$)-CH=CH-$CH_2$-OTBDPS), 4.37 (ddd, *J* = 27.7, 14.7, 6.7 Hz, 1H, (P)O-$CH_a$<u>H$_b$</u>-CH=CH-), 4.23 – 4.16 (m, 2H, -CH=CH-C<u>H$_2$</u>-OTBDPS), 2.43 (dtd, *J* = 6.9, 4.5, 2.4 Hz, 1H, -C<u>H</u>($CH_3$)-CH=CH-$CH_2$-OTBDPS), 2.15 (ddd, *J* = 14.6, 12.0, 6.3 Hz, 1H, (P)O-CH-C<u>H$_a$</u>$H_b$-CH-O(P)), 1.57 – 1.49 (m, 1H, (P)O-CH-$CH_a$<u>H$_b$</u>-CH-O(P)), 1.10 (d, *J* = 6.9 Hz, 3H, -CH(C<u>H$_3$</u>)-CH=CH-$CH_2$-OTBDPS), 1.06 (s, 9H, -OSi$(Ph)_2$-C(C<u>H$_3$</u>)$_3$);

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 135.5 (aromatic CH x 4), 133.70 (aromatic C), 133.66 (aromatic C), 131.4 (CH), 129.9 (CH), 129.8 (CH), 129.7 (aromatic CH x 2), 127.9 (CH), 127.64 (aromatic CH x 2), 127.63 (aromatic CH x 2), 79.4 (d, $J_{CP}$ = 7.0 Hz, CH), 77.1 (CH), 64.3 ($CH_2$), 63.0 (d, $J_{CP}$ = 6.4 Hz, $CH_2$), 40.9 (d, $J_{CP}$ = 8.8 Hz, CH), 31.7 (d, $J_{CP}$ = 5.7 Hz, $CH_2$), 26.8 (Si-C(<u>C</u>$H_3$)$_3$), 19.2 (Si-<u>C</u>($CH_3$)$_3$), 15.5 ($CH_3$);

**$^{31}$P NMR** (162 MHz, $CDCl_3$) δ -3.50 (t, *J* = 26.1 Hz);

**HRMS** cald for $C_{27}H_{35}O_5PSiNa$ $(M+Na)^+$ 521.1889; found 521.1895 (TOF MS ES+).

**(4*R*,6*R*)-4-((*S*)-but-3-en-2-yl)-6-((*R*,*E*)-5-((*tert*-butyldiphenylsilyl)oxy)pent-3-en-2-yl)-2-methoxy-1,3,2-dioxaphosphinane 2-oxide ($C_{29}H_{41}O_5PSi$, 3.14.7-SI)**




**3.14.7-SI**

In a glovebox, under argon, CuCN (28.0 mg, 0.311 mmol) and LiCl (26.0 mg, 0.622 mmol) were added to a pear-shaped flask equipped with a magnetic stirbar. The flask was capped with a rubber septum, removed from the glovebox, and equipped with an argon inlet. THF (0.62 mL) was added the flask, and the mix stirred at room temperature to dissolve all solids (~25 min). The flask was cooled to an external temperature of -30°C, and $Me_2Zn$ (0.31 mL, 1.0 M in hexanes) was added to the reaction mixture, drop-wise, slowly. The mix continued to stir at -30°C for 1 hour to generate the active (dimethyl)cyanocuprate. The flask was then cooled to -40°C, where **3.14.3** (31 mg, 0.062 mmol) in THF (0.31 mL) was added, drop-wise, slowly. The reaction was removed from the cooling bath and allowed to warm to room temperature, where it stirred for 2 hours (complete by TLC). The reaction was quenched with saturated $NH_4Cl$ (aq, 1 mL), diluted with EtOAc (3 mL), and vigorously stirred, open to air, for 1 hour. The reaction mixture was filtered over celite, dried over sodium sulfate, filtered over celite, and concentrated under reduced pressure. The crude material was taken up in MeOH (0.6 mL), and TMS-diazomethane (124 mL, 2.0 M in diethyl ether) was added dropwise, slowly, at room temperature. (Note: when added too quickly, the TMS-diazomethane will cause the reaction to heat and effervesce. For large batches—or small, the reaction flask can be

cooled to 0°C to control the fluctuation of temperature and decrease the sensitivity of the reaction to the rate of addition of TMS-diazomethane.) The reaction stirred for 12 H, where another 4 equivalents of TMS-diazomethane (124 mL, 2.0 M in diethyl ether) was added, and the reaction stirred for 1 hour at room temperature (complete by TLC). Excess TMS-diazomethane was quenched with 3 drops of glacial acetic acid, and the reaction was diluted with EtOAc (3 mL) and stirred at room temperature for 10 minutes (Note: complete quench is accompanied by a color change—from deep yellow to colorless). The mix was then dried over $Na_2SO_4$, filtered over celite (pipette filter), and concentrated under reduced pressure. The crude mix was separated by flash chromatography (silica, 0-100% EtOAc in hexanes) and title compound **3.14.7-SI** (18.0 mg, 0.0341 mmol, 55% yield) was isolated as a colorless oil and an inseparable mixture of diastereomers at the chiral phosphorus (dr ~ 1:1).

**FTIR** (neat): 2961, 2932, 1462, 1427, 1379, 1288, 1111, 1030, 972, 924, 856, 822, 741, 702, 611, 504 $cm^{-1}$;

**Optical Rotation**: $[\alpha]_D = -4.2$ ($c = 0.85$, $CHCl_3$);

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.66 (dq, $J$ = 8.2, 1.7 Hz, 8H), 7.46 – 7.36 (m, 12H), 5.85 – 5.73 (m, 2H), 5.63 (ddtd, $J$ = 15.4, 13.7, 4.7, 0.8 Hz, 2H), 5.51 (ddt, $J$ = 15.3, 8.5, 1.7 Hz, 1H), 5.43 (ddt, $J$ = 15.3, 8.7, 1.7 Hz, 1H), 5.13 – 5.05 (m, 4H), 4.41 (tdd, $J$ = 8.0, 6.2, 4.5 Hz, 1H), 4.28 (ddt, $J$ = 10.0, 5.1, 3.1 Hz, 1H), 4.24 – 4.08 (m, 6H), 3.81 (d, $J$ = 4.7 Hz, 3H), 3.79 (d, $J$ = 4.8 Hz, 3H), 2.65 (tt, $J$ = 12.8, 4.6 Hz, 1H), 2.58 (ddt, $J$ = 15.2, 8.6, 6.8 Hz, 1H), 2.54 – 2.45 (m, 1H), 2.43 – 2.34 (m, 1H), 2.04 – 1.95 (m, 2H), 1.91 (dddd, $J$

= 14.8, 6.4, 4.5, 1.7 Hz, 1H), 1.87 – 1.80 (m, 1H), 1.15 (dd, $J$ = 6.6, 5.5 Hz, 6H), 1.09 – 1.01 (m, 24H);

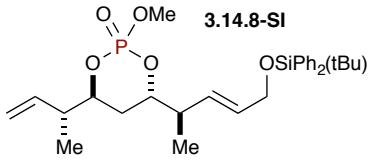
**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 138.3, 137.8, 135.5 (2 x 4 aromatic CH), 133.54 (2 x aromatic C), 133.52, 133.51, 131.22, 131.21, 130.5, 130.2, 129.72 (2 x aromatic CH), 129.69 (2 x aromatic CH), 127.7 (2 x 4 aromatic CH), 116.7, 116.4, 81.9 (d, $J_{CP}$ = 7.0 Hz), 80.3 (d, $J_{CP}$ = 6.8 Hz), 80.0 (d, $J_{CP}$ = 6.3 Hz), 78.9 (d, $J_{CP}$ = 6.8 Hz), 63.95, 63.92, 54.36 (dd, $J_{CP}$ = 6.0, 2.2 Hz), 54.04 (d, $J_{CP}$ = 5.8 Hz), 42.5 (d, $J_{CP}$ = 7.8 Hz), 41.8 (d, $J_{CP}$ = 5.5 Hz), 41.5 (d, $J_{CP}$ = 6.3 Hz), 40.5 (d, $J_{CP}$ = 2.8 Hz), 30.2 (d, $J_{CP}$ = 6.3 Hz), 30.0 (d, $J_{CP}$ = 6.1 Hz), 26.8 (2 x Si-C($\underline{C}H_3)_3$), 19.2 (2 x Si-$\underline{C}(CH_3)_3$), 17.2, 16.7, 15.9, 15.5;

**$^{31}$P NMR** (162 MHz, $CDCl_3$) δ -4.48 (q, $J$ = 9.6 Hz), -4.67 – -5.10 (m);

**$^{31}$P NMR-{1H}** (162 MHz, $CDCl_3$) δ -4.48, -4.89;

**HRMS** cald for $C_{29}H_{41}O_5PSiK$ $(M+K)^+$ 567.2098; found 567.2089 (TOF MS ES+).

**(4*S*,6*S*)-4-((*R*)-but-3-en-2-yl)-6-((*R*,*E*)-5-((*tert*-butyldiphenylsilyl)oxy)pent-3-en-2-yl)-2-methoxy-1,3,2-dioxaphosphinane 2-oxide ($C_{29}H_{41}O_5PSi$, 3.14.8-SI)**




**3.14.8-SI**

In a glovebox, under argon, CuCN (40.0 mg, 0.441 mmol) and LiCl (37.0 mg, 0.882 mmol) were added to a pear-shaped flask equipped with a magnetic stirbar. The flask was capped with a rubber septum, removed from the glovebox, and equipped with an argon inlet. THF (0.88 mL) was added the flask, and the mix stirred at room temperature to dissolve all solids (~25 min). The flask was cooled to an external temperature of -30°C, and $Me_2Zn$ (0.44 mL, 1.0 M in hexanes) was added to the reaction mixture, drop-wise, slowly. The mix continued to stir at -30°C for 1 hour to generate the active (dimethyl)cyanocuprate. The flask was then cooled to -40°C, where **3.14.6-SI** (44 mg, 0.0882 mmol) in THF (0.88 mL) was added, drop-wise, slowly. The reaction was removed from the cooling bath and allowed to warm to room temperature, where it stirred for 2 hours (complete by TLC). The reaction was quenched with saturated $NH_4Cl$ (aq, 1 mL), diluted with EtOAc (1 mL), and stirred open to air for 1 hour. The reaction mixture was filtered over celite, dried over sodium sulfate, filtered over celite, and concentrated under reduced pressure. The crude material was taken up in MeOH (0.9 mL), and TMS-diazomethane (180 mL, 2.0 M in diethyl ether) was added dropwise, slowly, at room temperature. (Note: when added too quickly, the TMS-diazomethane will cause the reaction to heat and effervesce. For large batches—or small, the reaction flask

can be cooled to 0°C to control the fluctuation of temperature and decrease the sensitivity of the reaction to the rate of addition of TMS-diazomethane.) The reaction stirred for 12 hours, where another 4 equivalents of TMS-diazomethane (180 mL, 2.0 M in diethyl ether) was added, and the reaction stirred for 1 hour at room temperature (complete by TLC). Excess TMS-diazomethane was quenched with 3 drops of glacial acetic acid, and the reaction was diluted with EtOAc (2 mL) and stirred at room temperature for 10 minutes (Note: complete quench is accompanied by a color change—from deep yellow to colorless). The mix was then dried over $Na_2SO_4$, filtered over celite (pipette filter), and concentrated under reduced pressure. The crude mix was separated by flash chromatography (silica, 0-100% EtOAc in hexanes) and title compound **3.14.8-SI** (26.0 mg, 0.0492 mmol, 56% yield) was isolated as a colorless oil and an inseparable mixture of diastereomers at the chiral phosphorus (dr ~ 1:1).

**FTIR** (neat): 2961, 2930, 1454, 1427, 1288, 1186, 1113, 1086, 1024, 972, 924, 852, 824, 743, 704, 613, 505 $cm^{-1}$;

**Optical Rotation**: $[\alpha]_D$ = +25.7 (*c* = 0.74, $CHCl_3$);

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.71 – 7.65 (m, 8H), 7.47 – 7.36 (m, 12H), 5.82 (dddd, *J* = 17.0, 10.5, 9.1, 7.7 Hz, 2H), 5.73 – 5.59 (m, 4H), 5.16 – 5.07 (m, 4H), 4.36 (ttd, *J* = 9.9, 6.4, 5.3 Hz, 2H), 4.30 – 4.23 (m, 2H), 4.20 (dt, *J* = 3.2, 1.4 Hz, 4H), 3.78 (d, *J* = 11.2 Hz, 3H), 3.76 (d, *J* = 11.3 Hz, 3H), 2.59 – 2.52 (m, 2H), 2.50 – 2.43 (m, 2H), 2.02 – 1.83 (m, 4H), 1.12 – 1.00 (m, 30H);

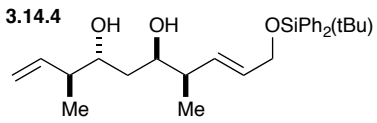
**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 138.5, 137.9 (2 x 4 aromatic CH), 135.5, 133.66, 133.61 (3 x aromatic C), 131.2, 130.8, 130.3, 129.8, 129.6 (4 x aromatic CH), 127.6 (2 x 4 aromatic CH), 116.7, 116.3, 80.55 (d, $J_{CP}$ = 6.5 Hz), 80.47 (d, $J_{CP}$ = 6.5 Hz), 79.3 (d, $J_{CP}$ = 4.8 Hz), 79.2 (d, $J_{CP}$ = 4.6 Hz), 64.3, 64.2, 54.27 (d, $J_{CP}$ = 2.8 Hz), 54.23 (d, $J_{CP}$ = 2.7 Hz), 42.5 (d, $J_{CP}$ = 7.8 Hz), 41.5 (d, $J_{CP}$ = 5.3 Hz), 41.2 (d, $J_{CP}$ = 8.2 Hz), 40.3 (d, $J_{CP}$ = 5.4 Hz), 30.0 (d, $J_{CP}$ = 5.7 Hz), 29.9 (d, $J_{CP}$ = 5.4 Hz), 26.81 (Si-C($\underline{C}H_3)_3$), 26.78 (Si-C($\underline{C}H_3)_3$), 19.2 (2 x Si-$\underline{C}(CH_3)_3$), 16.4, 16.0, 15.7, 15.5;

**$^{31}$P NMR** (162 MHz, $CDCl_3$) δ -3.28 – -4.00 (m);

**$^{31}$P NMR-{1H}** (162 MHz, $CDCl_3$) δ -3.50, -3.67;

**HRMS** cald for $C_{29}H_{41}O_5PSiNa$ $(M+Na)^+$ 551.2359; found 551.2364 (TOF MS ES+).

**(3*S*,4*R*,6*R*,7*R*,*E*)-10-((*tert*-butyldiphenylsilyl)oxy)-3,7-dimethyldeca-1,8-diene-4,6-diol ($C_{28}H_{40}O_3Si$, 3.14.4)**




To a stirring solution of **3.14.7-SI** (24 mg, 0.045 mmol) in THF (0.5 mL) under argon was added $LiAlH_4$ (4.7 mg, 0.12 mmol) in one portion at 0 °C. The reaction stirred at 0 °C for 1 hour (complete by TLC), at which point the reaction was diluted with EtOAc (~1 mL) and quenched by the sequential additions of $H_2O$ and 10% NaOH (wt.%, aq) [4.7 mL $H_2O$, 4.7 mL NaOH solution, 14.1 mL $H_2O$]. The mixture was allowed to warm to room temperature and stir at room temperature for 2 hours (white precipitate formed).

The reaction was filtered over celite (wash with EtOAc, dichloromethane, and MeOH) and concentrated under reduced pressure. Purification via flash chromatography provided the corresponding diol (**3.14.4**, 17.0 mg, 0.038 mmol, 83% yield) as a colorless oil.

**FTIR** (neat): 3398 (br), 3070, 2959, 2930, 2893, 1462, 1427, 1377, 1111, 999, 972, 914, 822, 702, 611, 505 $cm^{-1}$;

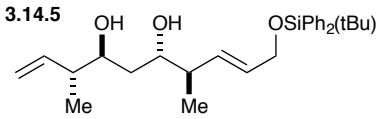
**Optical Rotation**: $[\alpha]_D = +10.9$ ($c = 0.17$, $CHCl_3$);

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.71 – 7.66 (m, 4H, aromatic C-H x 4), 7.47 – 7.36 (m, 6H, aromatic C-H x 6), 5.73 (ddd, *J* = 17.9, 9.8, 8.4 Hz, 1H, -CH(OH)-CH($CH_3$)-C<u>H</u>=$CH_2$), 5.63 – 5.58 (m, 2H, -CH(OH)-CH($CH_3$)-C<u>H</u>=C<u>H</u>-$CH_2$-OTBDPS), 5.18 – 5.12 (m, 2H, -CH(OH)-CH($CH_3$)-CH=C<u>H</u>$_2$), 4.19 (d, *J* = 3.7 Hz, 2H, -CH=CH-C<u>H</u>$_2$-OTBDPS), 3.71 (dtd, *J* = 20.8, 7.2, 3.4 Hz, 2H, -C<u>H</u>(OH)-$CH_2$-C<u>H</u>(OH)-), 2.43 (d, *J* = 5.1 Hz, 1H, O-<u>H</u>), 2.31 (q, *J* = 6.7 Hz, 1H, -C<u>H</u>($CH_3$)-CH=CH-$CH_2$-OTBDPS), 2.24 (dt, *J* = 8.2, 6.8 Hz, 1H, -CH(OH)-C<u>H</u>($CH_3$)-CH=$CH_2$), 2.11 (d, *J* = 3.3 Hz, 1H, O-<u>H</u>), 1.62 (ddd, *J* = 7.5, 5.7, 3.3 Hz, 2H, -CH(OH)-C<u>H</u>$_2$-CH(OH)-), 1.09 – 1.03 (M, 12H, -OSi(Ph)$_2$-C(C<u>H</u>$_3$)$_3$, -CH(OH)-CH(C<u>H</u>$_3$)-CH=CH-$CH_2$-), 1.00 (d, *J* = 6.8 Hz, 3H, -CH(OH)-CH(C<u>H</u>$_3$)-CH=$CH_2$);

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 140.5 (CH), 135.6 (4 x aromatic CH), 133.78 (aromatic C), 133.76 (aromatic C), 132.7 (CH), 129.9 (CH), 129.6 (2 x aromatic CH), 127.6 (4 x aromatic CH), 116.9 ($CH_2$), 72.2 (CH), 72.1 (CH), 64.4 ($CH_2$), 44.5 (CH), 42.5 (CH), 36.6 ($CH_2$), 26.8 (Si-C(<u>C</u>$H_3$)$_3$), 19.2 (Si-<u>C</u>($CH_3$)$_3$), 16.3 ($CH_3$), 15.9 ($CH_3$);

**HRMS** cald for $C_{28}H_{40}O_3SiK$ $(M+K)^+$ 491.2384; found 491.2382 (TOF MS ES+).

**(3*R*,4*S*,6*S*,7*R*,*E*)-10-((*tert*-butyldiphenylsilyl)oxy)-3,7-dimethyldeca-1,8-diene-4,6-diol ($C_{28}H_{40}O_3Si$, 3.14.5)**




To a stirring solution of **3.14.8-SI** (30 mg, 0.057 mmol) in THF (1 mL) under argon was added $LiAlH_4$ (4.3 mg, 0.11 mmol) in one portion at 0 $^oC$. The reaction stirred at 0 $^oC$ for 1 hour (complete by TLC), at which point the reaction was diluted with EtOAc (~1 mL) and quenched by the sequential additions of $H_2O$ and 10% NaOH (wt.%, aq) [4.3 mL $H_2O$, 4.3 mL NaOH solution, 12.9 mL $H_2O$]. The mixture was allowed to warm to room temperature and stir at room temperature for 2 hours (white precipitate formed). The reaction was filtered over celite (wash with EtOAc, dichloromethane, and MeOH) and concentrated under reduced pressure. Purification via flash chromatography provided the corresponding diol (**3.14.5**, 22 mg, 0.049 mmol, 86% yield) as a colorless oil.

**FTIR** (neat): 3412 (br), 2959, 2930, 1462, 1427, 1379, 1111, 997, 974, 914, 739, 702, 613, 503 $cm^{-1}$;

**Optical Rotation**: $[\alpha]_D$ = +11.4 (*c* = 0.22, $CHCl_3$);

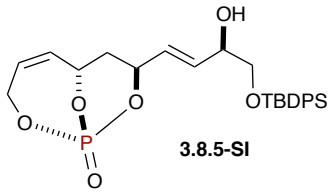
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.71 – 7.65 (m, 4H, aromatic C-H x 4), 7.47 – 7.36 (m, 6H, aromatic C-H x 6), 5.83 – 5.73 (m, 1H, -CH(OH)-CH($CH_3$)-C<u>H</u>=$CH_2$), 5.67 (dt, *J* = 15.5, 4.6 Hz, 1H, -CH(OH)-CH($CH_3$)-CH=C<u>H</u>-$CH_2$-OTBDPS), 5.59 (ddt, *J* = 15.4, 8.1, 1.4 Hz, 1H, -CH(OH)-CH($CH_3$)-C<u>H</u>=CH-$CH_2$-OTBDPS), 5.13 (dqd, *J* = 13.7, 1.9, 1.0 Hz, 2H, -CH(OH)-CH($CH_3$)-CH=C<u>H$_2$</u>), 4.21 (dd, *J* = 4.6, 1.4 Hz, 2H, -CH=CH-C<u>H$_2$</u>-

OTBDPS), 3.80 – 3.59 (m, 2H, -C<u>H</u>(OH)-$CH_2$-C<u>H</u>(OH)-), 2.41 (d, *J* = 3.3 Hz, 1H, O-<u>H</u>), 2.26 (dddd, *J* = 14.0, 6.9, 3.0, 1.4 Hz, 2H, -CH(OH)-C<u>H</u>($CH_3$)-CH=$CH_2$, -CH(OH)-C<u>H</u>($CH_3$)-CH=CH-$CH_2$-OTBDPS), 2.19 (d, *J* = 3.1 Hz, 1H, O-<u>H</u>), 1.63 (dt, *J* = 7.5, 3.5 Hz, 2H, -CH(OH)-C<u>H</u>$_2$-CH(OH)-), 1.07 (s, 9H, -OSi(Ph)$_2$-C(C<u>H</u>$_3$)$_3$), 1.03 (d, *J* = 6.8 Hz, 3H, -CH(OH)-CH(C<u>H</u>$_3$)-), 1.00 (d, *J* = 6.8 Hz, 3H, -CH(OH)-CH(C<u>H</u>$_3$)-);

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 140.7 (CH), 135.5 (4 x aromatic CH), 133.72 (aromatic C), 133.71 (aromatic C), 132.3 (CH), 131.2 (CH), 129.7 (2 x aromatic CH), 127.7 (4 x aromatic CH), 116.3 ($CH_2$), 72.0 (CH), 71.8 (CH), 64.3 ($CH_2$), 44.3 (CH), 42.9 (CH), 36.4 ($CH_2$), 26.9 (Si-C(<u>C</u>$H_3$)$_3$), 19.2 (Si-<u>C</u>($CH_3$)$_3$), 16.4 ($CH_3$), 16.1 ($CH_3$);

**HRMS** cald for $C_{28}H_{40}O_3SiK$ $(M+K)^+$ 491.2384; found 491.2381 (TOF MS ES+).

**(1*R*,6*S*,8*S*)-8-((*R*,*E*)-4-((*tert*-butyldiphenylsilyl)oxy)-3-hydroxybut-1-en-1-yl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-oxide ($C_{26}H_{33}O_6PSi$, 3.8.5-SI)**




3.8.5-SI

To a stirring solution of ($S_P$,*S*,*S*)-bicyclic phosphate[5] **3.8.2** (95 mg, 0.47 mmol) under argon was added dry, degassed methylene chloride (4.7 mL), (*R*)-1-((*tert*-butyldiphenylsilyl)oxy)but-3-en-2-ol[8] (461 mg, 1.41 mmol), *p*-benzoquinone (5.1 mg, 0.047 mmol), then Hoveyda-Grubbs second generation catalyst (8.8 mg, 0.0141 mmol, 3 mol %), and the reaction was heated to reflux. The reaction stirred at reflux for 3 hours, where additional Hoveyda-Grubbs second-generation catalyst (14.1 mg, 0.0225 mmol, 3

mol %) was added. The reaction continued to stir for 18 hours (progression stalled by TLC). The reaction was concentrated under reduced pressure, and the crude mixture was purified via flash chromatography (silica, 0%–100% EtOAc in hexanes) to provide title **3.8.5-SI** (0.136 g, 0.272 mmol, 58% yield) as an off-white foam.

**FTIR** (neat): 3398 (br), 3070, 2930, 2856, 1462, 1427, 1294, 1113, 1067, 1036, 997, 968, 922, 883, 824, 775, 744, 704, 613 505, 490 $cm^{-1}$;

**Optical Rotation**: $[\alpha]_D$ = +49.0 (*c* = 0.26, $CHCl_3$);

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.68 – 7.62 (m, 4H, aromatic C-H x 4), 7.48 – 7.37 (m, 6H, aromatic C-H x 6), 6.05 (dddd, *J* = 11.9, 6.7, 3.1, 2.1 Hz, 1H, (P)O-CH-CH=C$\underline{H}$-$CH_2$-O(P)), 5.88 – 5.76 (m, 2H, -C$\underline{H}$=C$\underline{H}$-CH(OH)-$CH_2$OTBDPS), 5.60 (ddd, *J* = 11.9, 4.0, 2.6 Hz, 1H, (P)O-CH-C$\underline{H}$=CH-$CH_2$-O(P)), 5.18 (dddt, *J* = 24.5, 6.1, 3.7, 1.9 Hz, 1H, (P)O-C$\underline{H}$-CH=CH-$CH_2$-O(P)), 5.07 – 4.96 (m, 2H, -$CH_2$-(P)O-C$\underline{H}$-CH=CH-CH(OH)-$CH_2$OTBDPS, (P)O-C$\underline{H}_a$$H_b$-CH=CH-), 4.38 (ddd, *J* = 27.7, 14.9, 7.1 Hz, 1H, (P)O-C$H_a$$\underline{H}_b$-CH=CH-), 4.28 (dt, *J* = 7.1, 3.6 Hz, 1H, -CH=CH-C$\underline{H}$(OH)-$CH_2$OTBDPS), 3.71 (dd, *J* = 10.3, 3.7 Hz, 1H, -CH=CH-CH(OH)-C$\underline{H}_a$$H_b$OTBDPS), 3.53 (dd, *J* = 10.2, 7.3 Hz, 1H, -CH=CH-CH(OH)-C$H_a$$\underline{H}_b$OTBDPS), 2.69 (s, 1H, -CH=CH-CH(O$\underline{H}$)-$CH_2$OTBDPS), 2.20 (ddd, *J* = 14.8, 12.0, 6.2 Hz, 1H, (P)O-CH-C$\underline{H}_a$$H_b$-CH-O(P)), 1.75 (dq, *J* = 14.7, 2.0 Hz, 1H, (P)O-CH-C$H_a$$\underline{H}_b$-CH-O(P)), 1.08 (s, 9H, -OSi$(Ph)_2$-C$(C\underline{H}_3)_3$);

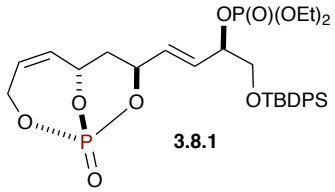
**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 135.52 (Aromatic CH x 2), 135.48 (Aromatic CH x 2), 132.9 (Aromatic C), 132.8 (Aromatic C), 131.6 (CH), 129.9 (Aromatic CH x 2), 129.6 (CH), 128.14 (CH), 128.06 (CH), 127.8 (Aromatic CH x 4), 76.9 (d, $J_{CP}$ = 6.6 Hz, CH),

75.5 (d, $J$ = 5.7 Hz, CH), 71.5 (CH), 67.4 ($CH_2$), 63.0 (d, $J_{CP}$ = 6.4 Hz, $CH_2$), 35.1 (d, $J_{CP}$ = 5.5 Hz, $CH_2$), 26.8 (Si-C($\underline{C}H_3$)$_3$), 19.2 (Si-$\underline{C}$($CH_3$)$_3$);

**$^{31}$P NMR** (162 MHz, $CDCl_3$) δ 0.85 – -9.88 (m);

**HRMS** cald for $C_{26}H_{33}O_6PSiNa$ $(M+Na)^+$ 523.1682; found 523.1699 (TOF MS ES+).

**(*R*,*E*)-1-((*tert*-butyldiphenylsilyl)oxy)-4-((1*R*,6*S*,8*S*)-1-oxido-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl)but-3-en-2-yl diethyl phosphate ($C_{30}H_{42}O_9P_2Si$, 3.8.1)**



3.8.1

To a solution of **3.8.5-SI** (56 mg, 0.119 mmol) in methylene chloride (dry, degassed, 1.1 mL) was added *N*,*N*-diisopropyl(ethyl)amine (39 mL, 0.224 mmol) under argon, and the reaction flask was cooled to an external temperature of -30$^o$C where diethylchlorophosphite (18 mL, 0.123 mmol) was added. The reaction was allowed to warm to 0 $^o$C over 30 minutes (complete conversion by TLC), where tBuOOH (25 mL, 5-6 M in decanes) was added. The reaction was allowed to warm to RT and continued to stir at room temperature for 2 hours (complete by TLC). Excess peroxide was quenched with solid sodium sulfite, and the heterogeneous mix stirred for 30 minutes to ensure a complete quench. The reaction was filtered over cotton, concentrated under reduced pressure, and purified via flash chromatography (silica, 50%–100% EtOAc in hexanes,

wash with 10% MeOH in EtOAc) to provide **3.8.1** (41.7 mg, 0.0655 mmol, 59% yield) as a colorless, viscous oil.

**FTIR** (neat): 3070, 3046, 2980, 2930, 2858, 1472, 1427, 1393, 1302, 1263, 1113, 1069, 1033, 997, 974, 924, 883, 822, 797, 743, 706, 613, 505 $cm^{-1}$;

**Optical Rotation**: $[\alpha]_D$ = +25.4 (*c* = 0.67, $CHCl_3$);

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.66 (dq, *J* = 6.5, 1.7 Hz, 4H, aromatic C-H x 4), 7.47 – 7.35 (m, 6H, aromatic C-H x 6), 6.07 (dddd, *J* = 11.8, 6.7, 3.1, 2.0 Hz, 1H, (P)O-CH-CH=C$\underline{H}$-$CH_2$-O(P)), 5.96 – 5.83 (m, 2H, -C$\underline{H}$=C$\underline{H}$-CH(O(PO(OEt)$_2$))-$CH_2$OTBDPS), 5.60 (ddd, *J* = 11.9, 4.1, 2.5 Hz, 1H, (P)O-CH-C$\underline{H}$=CH-$CH_2$-O(P)), 5.19 (ddq, *J* = 24.5, 6.5, 2.1 Hz, 1H, (P)O-C$\underline{H}$-CH=CH-$CH_2$-O(P)), 5.04 (dddt, *J* = 15.0, 12.1, 5.6, 2.3 Hz, 2H, -$CH_2$-(P)O-C$\underline{H}$-CH=CH-CH(O(P(O)(OEt)$_2$))-$CH_2$OTBDPS, -(P)O-C$\underline{H}_a$$H_b$-CH=CH-), 4.93 – 4.85 (m, 1H, -CH=CH-C$\underline{H}$(O(P(O)(OEt)$_2$))-$CH_2$OTBDPS), 4.40 (ddd, *J* = 27.8, 14.8, 6.7 Hz, 1H, -(P)O-$CH_a\underline{H}_b$-CH=CH-), 4.13 – 4.00 (m, 4H, -P(O)(OC$\underline{H}_2$$CH_3$)$_2$), 3.84 – 3.76 (m, 1H, -C$\underline{H}_a$$CH_b$-OTBDPS), 3.70 (ddd, *J* = 10.8, 5.2, 1.6 Hz, 1H, -$CH_a$C$\underline{H}_b$-OTBDPS), 2.18 (ddd, *J* = 14.8, 11.9, 6.2 Hz, 1H, (P)O-CH-C$\underline{H}_a$$H_b$-CH-O(P)), 1.76 (ddt, *J* = 14.7, 2.3, 1.2 Hz, 1H, (P)O-CH-$CH_a\underline{H}_b$-CH-O(P)), 1.29 (dtd, *J* = 15.3, 7.1, 1.1 Hz, 6H, -P(O)(OC$H_2$C$\underline{H}_3$)$_2$), 1.05 (d, *J* = 1.7 Hz, 9H, -OSi(Ph)$_2$-C(C$\underline{H}_3$)$_3$);

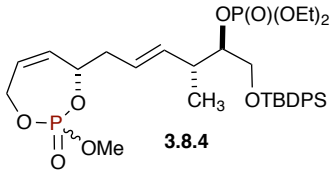
**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 135.56 (aromatic CH x 2), 135.52 (aromatic CH x 2), 132.97 (aromatic C), 132.91 (aromatic C), 130.3 (d, $J_{CP}$ = 10.4 Hz, CH), 129.84 (aromatic CH), 129.81 (aromatic CH), 129.5 (CH), 129.0 (d, $J_{CP}$ = 3.6 Hz, CH), 128.2 (CH), 127.75 (aromatic CH x 2), 127.74 (aromatic CH x 2), 77.8 (d, $J_{CP}$ = 5.6 Hz, CH),

76.90 (d, $J_{CP}$ = 6.7 Hz, CH), 75.1 (d, $J$ = 5.9 Hz, CH), 65.9 (d, $J_{CP}$ = 6.8 Hz, $CH_2$), 63.83 (d, $J_{CP}$ = 3.0 Hz, $CH_2$), 63.78 (d, $J_{CP}$ = 2.9 Hz, $CH_2$), 63.01 (d, $J$ = 6.4 Hz, $CH_2$), 35.0 (d, $J_{CP}$ = 5.8 Hz, $CH_2$), 26.7 (Si-C($\underline{C}H_3)_3$), 19.2 (Si-$\underline{C}(CH_3)_3$), 16.1 (d, $J_{CP}$ = 7.0 Hz, $CH_3$), 16.04 (d, $J_{CP}$ = 7.6 Hz, $CH_3$);

**$^{31}$P NMR** (162 MHz, $CDCl_3$) δ -1.77 (q, $J$ = 7.9 Hz), -4.48 (t, $J$ = 25.7 Hz);

**HRMS** cald for $C_{30}H_{42}O_9P_2SiNa$ $(M+Na)^+$ 659.1971; found 659.1974 (TOF MS ES+).

**(2*R*,3*R*,*E*)-1-((*tert*-butyldiphenylsilyl)oxy)-6-((4*S*)-2-methoxy-2-oxido-4,7-dihydro-1,3,2-dioxaphosphepin-4-yl)-3-methylhex-4-en-2-yl diethyl phosphate ($C_{32}H_{48}O_9P_2Si$, 3.8.4)**




**3.8.4**

In a glovebox, under argon, CuCN (9.0 mg, 0.094 mmol) and LiCl (8.0 mg, 0.19 mmol) were added to a pear-shaped flask equipped with a magnetic stirbar. The flask was capped with a rubber septum, removed from the glovebox, and equipped with an argon inlet. THF (0.19 mL) was added the flask, and the mix stirred at room temperature to dissolve all solids (~25 min). The flask was cooled to an external temperature of -30°C, and $Me_2Zn$ (0.09 mL, 1.0 M in hexanes) was added to the reaction mixture, drop-wise, slowly. The mix continued to stir at -30°C for 1 hour to generate the active (dimethyl)cyanocuprate. The flask was then cooled to -40°C, where **3.8.1** (20 mg, 0.031 mmol) in THF (0.31 mL) was added, drop-wise, slowly. The reaction stirred at -40°C to -

20°C while for 50 minutes (complete by TLC). The reaction was quenched with saturated $NH_4Cl$ (aq, 1 mL) and diluted with EtOAc (1 mL) at -20°C and vigorously stirred, open to air, while warming to +10°C over 1 H. The biphasic solution was separated, and the aqueous layer extracted with EtOAc [5 x 3 mL] doped with nBuOH [3-4 drops per mL EtOAc). The organic layers were combined, washed with saturated $NH_4Cl$ (2 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude material was taken up in MeOH (~0.4 mL), and TMS-diazomethane (0.05 mL, 2.0 M in diethyl ether) was added dropwise, slowly, at room temperature. (Note: when added too quickly, the TMS-diazomethane will cause the reaction to heat and effervesce. For large batches—or small, the reaction flask can be cooled to 0°C to control the fluctuation of temperature and decrease the sensitivity of the reaction to the rate of addition of TMS-diazomethane.) The reaction stirred for 12 H, where another 1.5 equivalents of TMS-diazomethane (25 mL) was added, and the reaction stirred for 1 hour at RT (complete by TLC). Excess TMS-diazomethane was quenched with 3 drops of glacial acetic acid, and the reaction was diluted with EtOAc (2 mL) and stirred at room temperature for 10 minutes (Note: complete quench is accompanied by a color change—from deep yellow to colorless). The mix was then dried over $Na_2SO_4$, filtered over celite (pipette filter), and concentrated under reduced pressure. The crude mix was separated by flash chromatography (silica, 0-100% EtOAc in hexanes) and title compound **3.8.4** (10.6 mg, 0.016 mmol, 52% yield) was isolated as a colorless oil and an inseparable mixture of diastereomers at the chiral phosphorus (dr ~ 1:1).

**FTIR** (neat): 2859, 2932, 2856, 1462, 1427, 1391, 1281, 1113, 1032, 824, 704, 613, 505 $cm^{-1}$;

**Optical Rotation**: $[\alpha]_D$ = + 15.2 (*c* = 0.27, $CHCl_3$);

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.66 (ddt, *J* = 7.8, 6.3, 1.5 Hz, 8H), 7.47 – 7.35 (m, 12H), 5.68 – 5.56 (m, 4H), 5.54 – 5.38 (m, 4H), 5.14 – 5.05 (m, 1H), 4.98 – 4.85 (m, 2H), 4.72 (ddq, *J* = 14.4, 8.5, 2.7 Hz, 1H), 4.57 – 4.39 (m, 2H), 4.34 (ddd, *J* = 10.0, 7.6, 4.8 Hz, 2H), 4.13 – 3.95 (m, 8H), 3.84 (dd, *J* = 11.1, 3.1 Hz, 6H), 3.78 (dtd, *J* = 11.3, 6.4, 5.8, 3.1 Hz, 2H), 3.71 – 3.61 (m, 2H), 2.76 (ddd, *J* = 12.0, 5.5, 3.0 Hz, 2H), 2.47 – 2.30 (m, 4H), 1.29 (tt, *J* = 7.1, 1.4 Hz, 6H), 1.23 (tt, *J* = 7.0, 1.3 Hz, 6H), 1.11 – 1.02 (m, 24H);

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 135.6 (aromatic CH x 4), 135.51 (aromatic CH x 4), 134.9 (CH), 134.8 (CH), 133.17 (aromatic C), 133.16 (aromatic C), 133.12 (aromatic C), 133.08 (aromatic C), 130.9 (CH), 130.2 (CH), 129.79 (aromatic CH), 129.76 (aromatic CH), 129.74 (aromatic CH x 2), 127.71 (aromatic CH x 4), 127.69 (aromatic CH x 4), 127.4 (CH), 126.3 (CH), 125.4 (CH), 125.1 (CH), 81.9 (d, $J_{CP}$ = 5.4 Hz, CH), 81.86 (d, $J_{CP}$ = 6.3 Hz, CH), 74.4 (d, $J_{CP}$ = 7.3 Hz, CH), 74.0 (d, $J_{CP}$ = 4.7 Hz, CH), 64.5 (d, $J_{CP}$ = 4.9 Hz, $CH_2$), 64.2 (d, $J_{CP}$ = 7.1 Hz, $CH_2$), 63.63 (d, $J_{CP}$ = 6.1 Hz, $CH_2$), 63.57 (d, $J_{CP}$ = 5.8 Hz, $CH_2$), 63.52 ($CH_2$), 63.49 ($CH_2$), 54.6 (d, $J_{CP}$ = 5.2 Hz, $CH_3$), 54.5 (d, $J_{CP}$ = 5.2 Hz, $CH_3$), 39.0 (d, $J_{CP}$ = 9.9 Hz, $CH_2$), 38.9 (d, $J_{CP}$ = 9.9 Hz, $CH_2$), 38.33 (d, $J_{CP}$ = 4.2 Hz, CH), 38.28 (d, $J_{CP}$ = 4.5 Hz, CH), 26.8 (-$Si(Ph_2)(C(\underline{C}H_3)_3$ x 2), 19.2 (-$Si(Ph_2)(\underline{C}(CH_3)_3$ x 2), 16.8 (-$CH_3$), 16.6 (-$CH_3$), 16.13 (d, $J_{CP}$ = 6.9 Hz, -$OP(O)(OCH_2\underline{C}H_3)_2$), 16.05 (d, $J_{CP}$ = 7.1 Hz, -$OP(O)(OCH_2\underline{C}H_3)_2$).

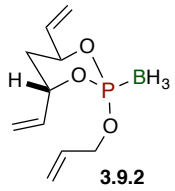
**$^{31}$P NMR** (162 MHz, $CDCl_3$) δ 3.16, -1.30 (d, $J$ = 8.1 Hz);

**$^{31}$P NMR-{$^{1}$H}** (162 MHz, $CDCl_3$) δ 3.20, 3.11, -1.30;

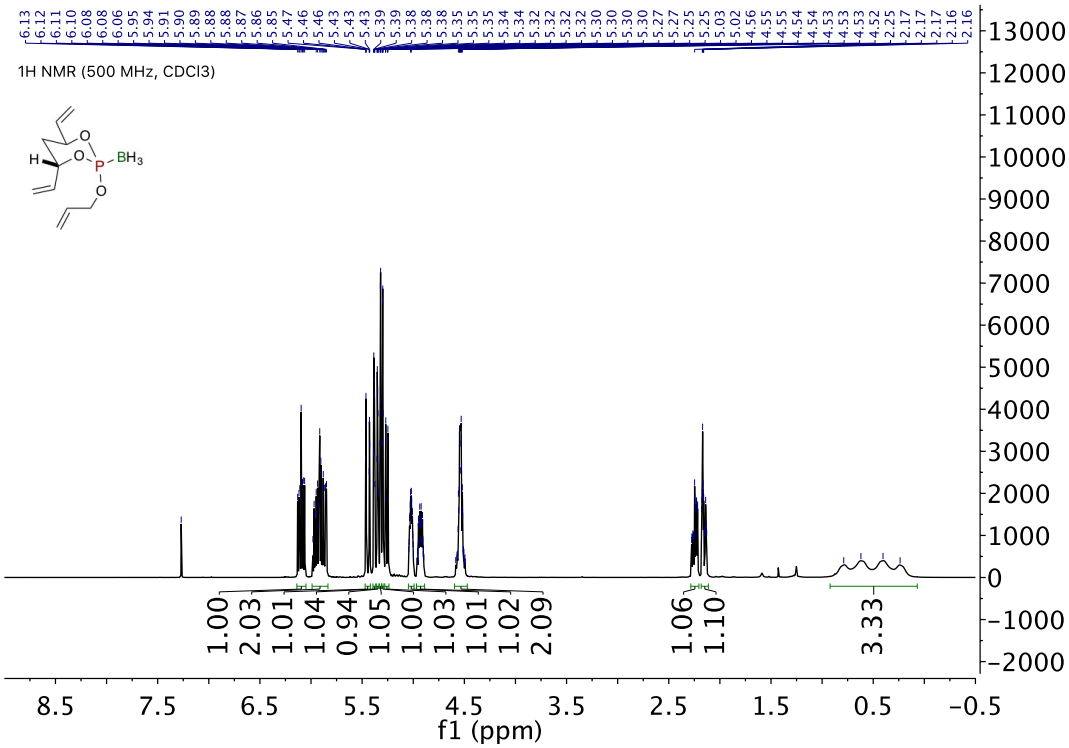
**HRMS** cald for $C_{32}H_{48}O_9P_2SiNa$ $(M+Na)^+$ 689.2441; found 689.2441 (TOF MS ES+).

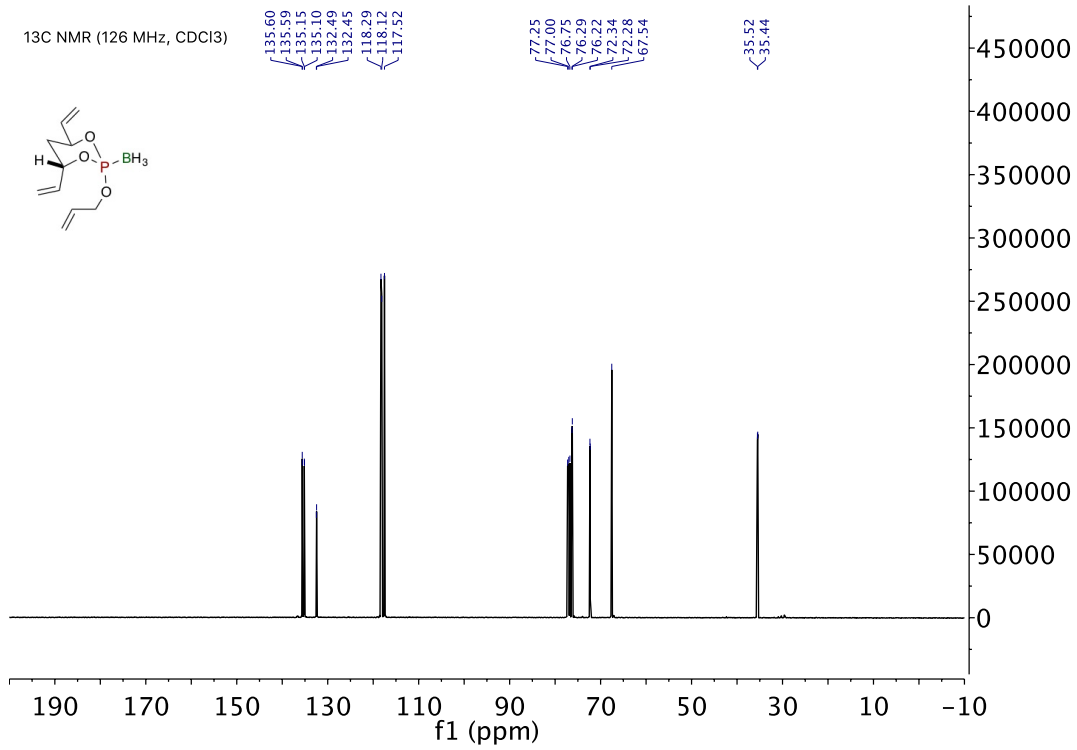
### 5.2.3 NMR Spectra

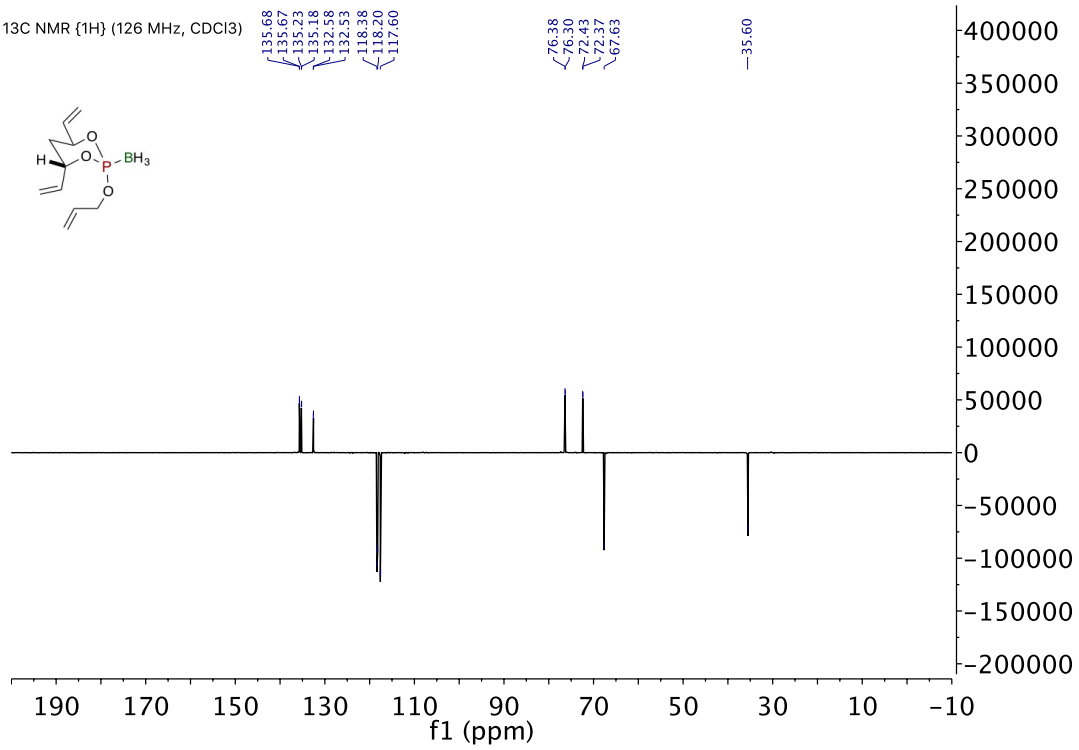
**(4*S*,6*S*)-2-(allyloxy)-4,6-divinyl-1,3,2-dioxaphosphite 1-borane ($C_{10}H_{18}BO_3P$, 3.9.2)**

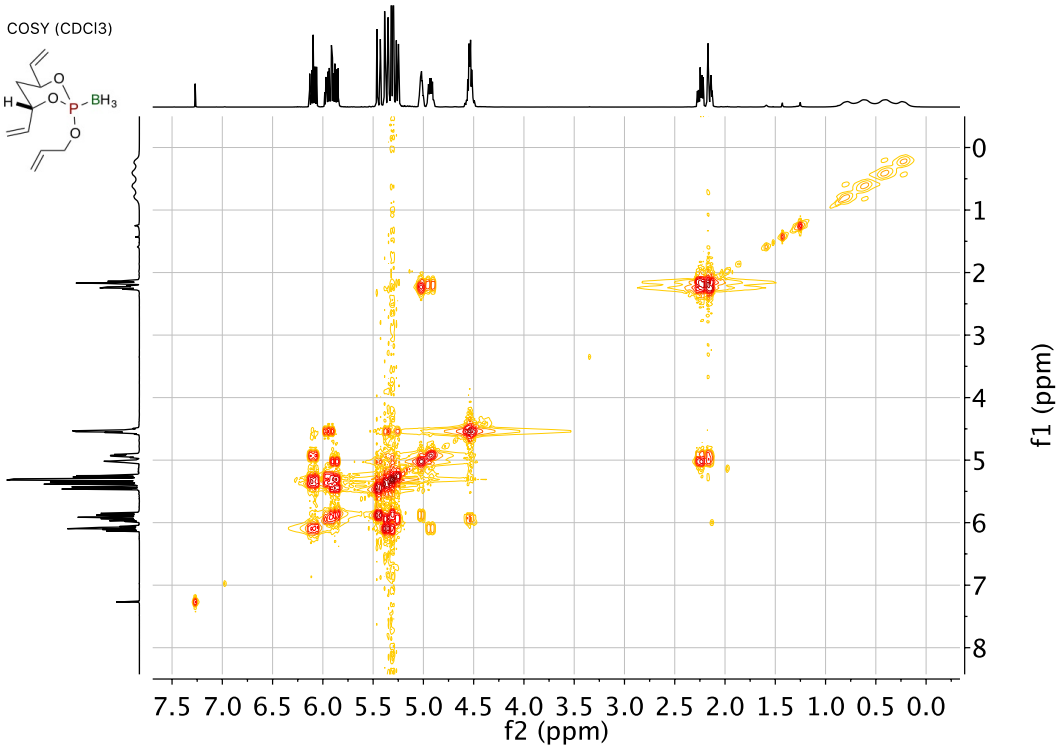


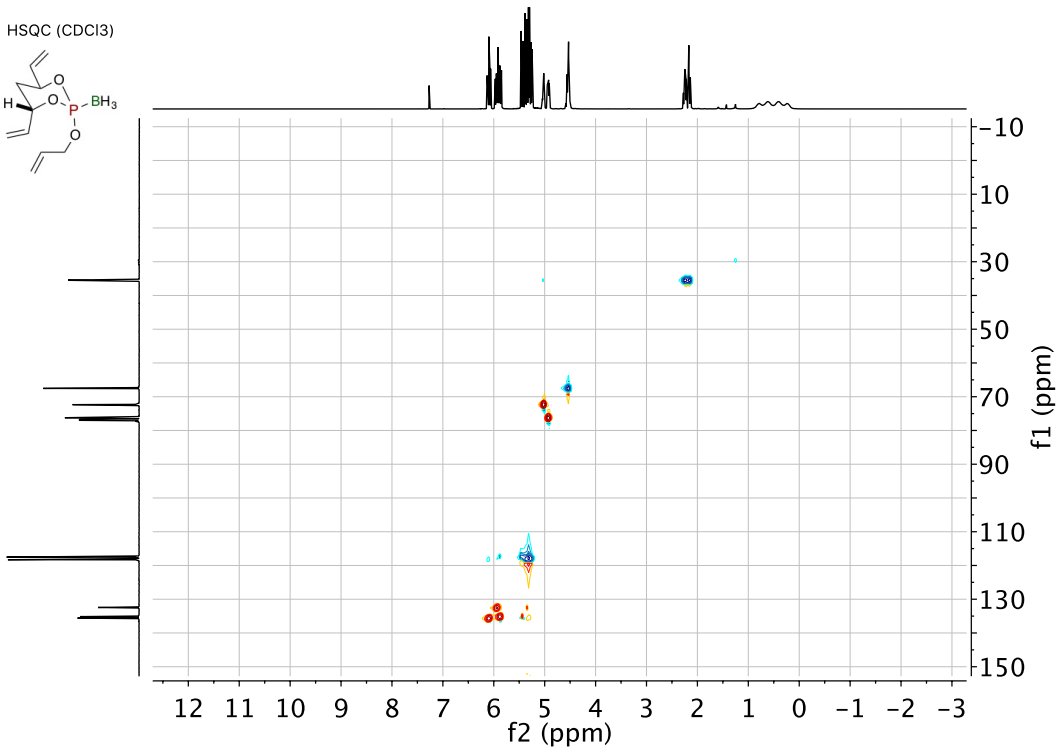

3.9.2

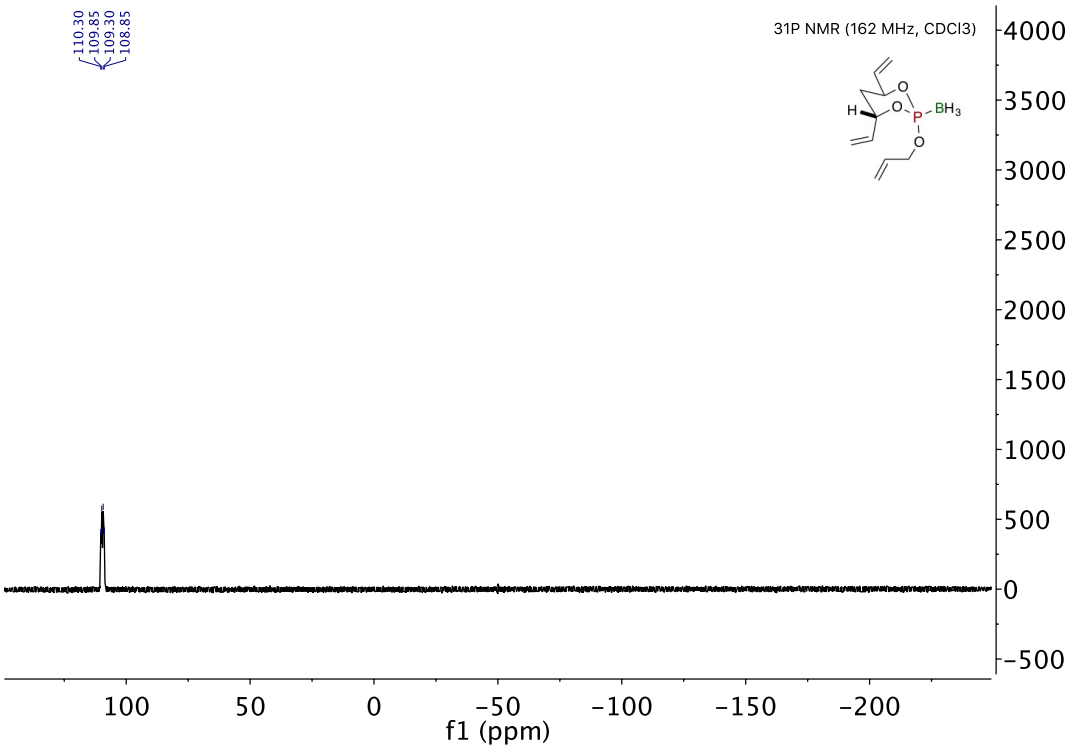


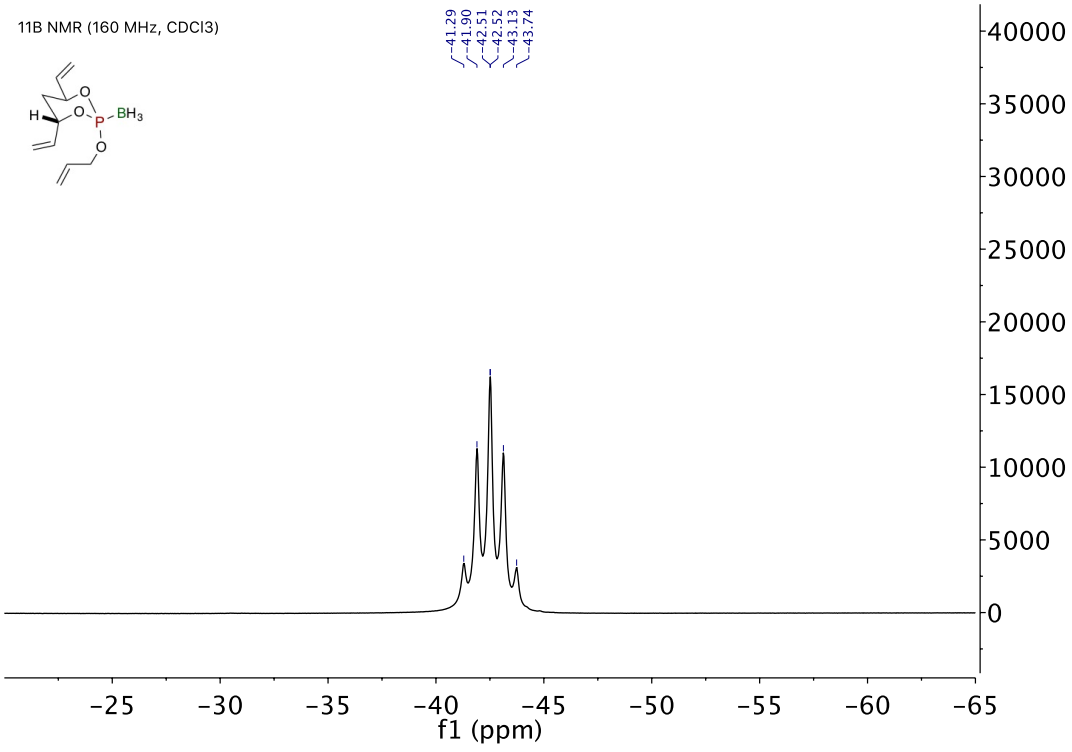

13C NMR (126 MHz, CDCl3)
135.60
135.59
135.15
135.10
132.49
132.45
118.29
118.12
117.52
77.25
77.00
76.75
76.29
76.22
72.34
72.28
67.54
35.52
35.44
450000
400000
350000
300000
250000
200000
150000
100000
50000
0
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)


13C NMR {1H} (126 MHz, CDCl3)
135.68
135.67
135.23
135.18
132.58
132.53
118.38
118.20
117.60
76.38
76.30
72.43
72.37
67.63
35.60
400000
350000
300000
250000
200000
150000
100000
50000
0
-50000
-100000
-150000
-200000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

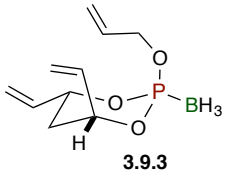

COSY (CDCl3)
H
O
O
P
BH3
O
0
1
2
3
4
5
6
7
8
f1 (ppm)
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f2 (ppm)


HSQC (CDCl3)
H
O
O
P
BH3
O
-10
10
30
50
70
90
110
130
150
f1 (ppm)
12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f2 (ppm)

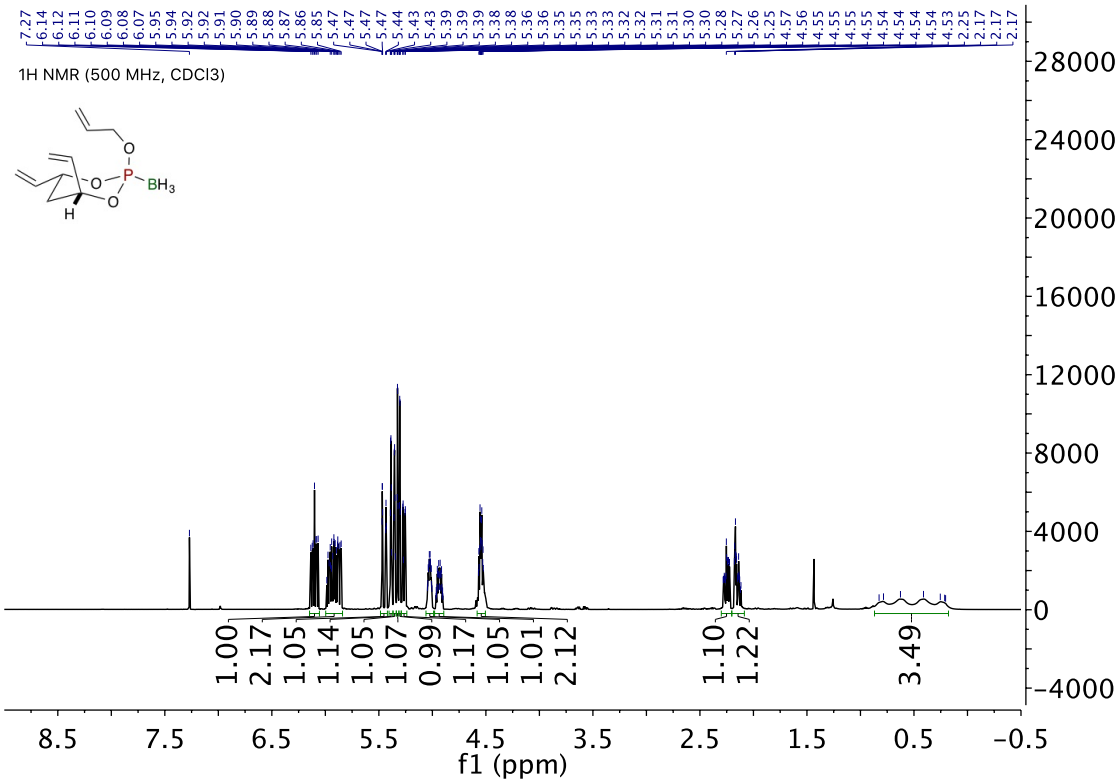

110.30
109.85
109.30
108.85
31P NMR (162 MHz, CDCl3)
4000
3500
3000
2500
2000
1500
1000
500
0
−500
100
50
0
−50
−100
−150
−200
f1 (ppm)

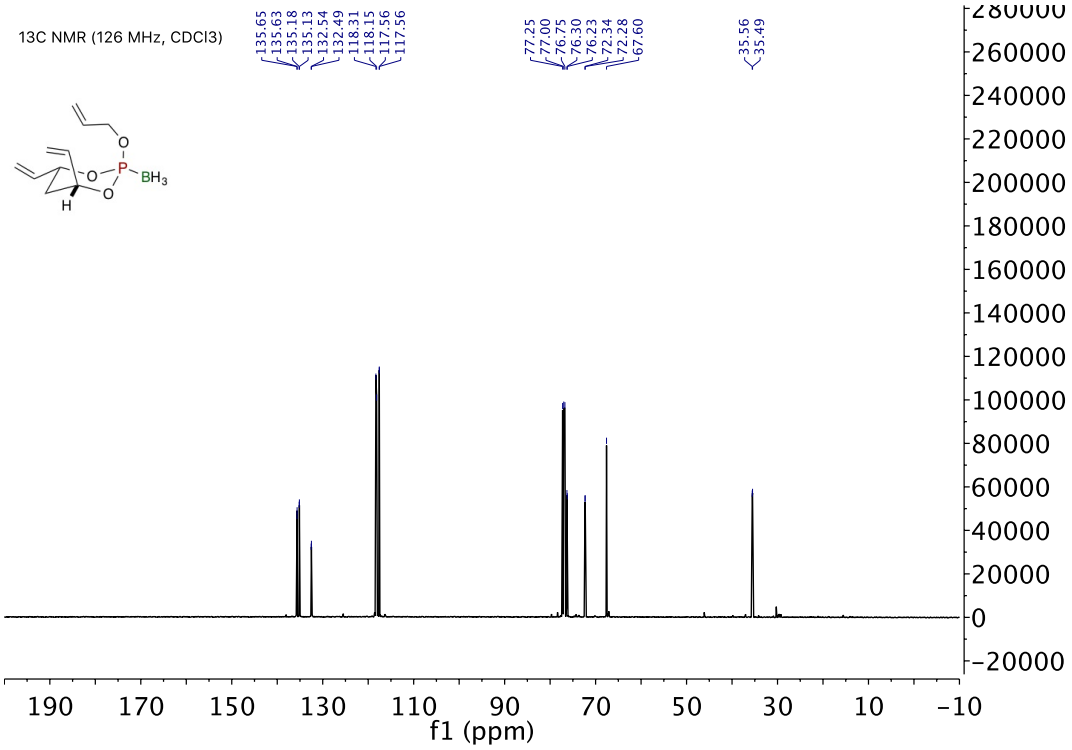

11B NMR (160 MHz, CDCl3)
−41.29
−41.90
−42.51
−42.52
−43.13
−43.74
40000
35000
30000
25000
20000
15000
10000
5000
0
−25
−30
−35
−40
−45
−50
−55
−60
−65
f1 (ppm)

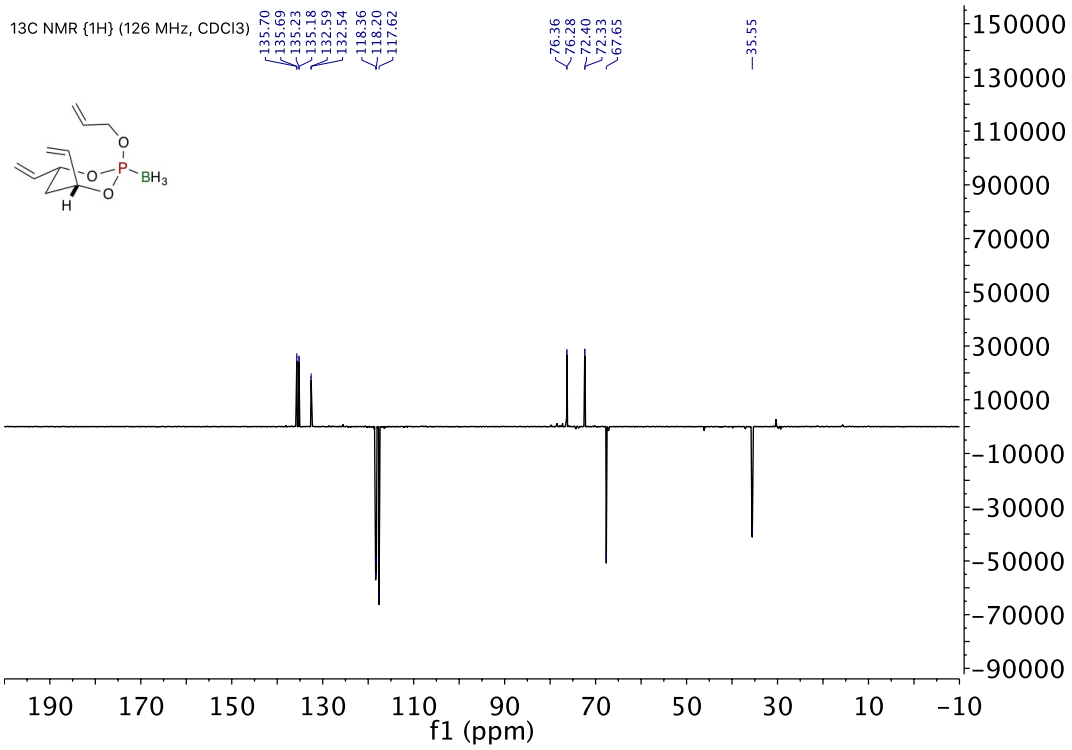
**(4*R*,6*R*)-2-(allyloxy)-4,6-divinyl-1,3,2-dioxaphosphite 1-borane ($C_{10}H_{18}BO_3P$, 3.9.3)**

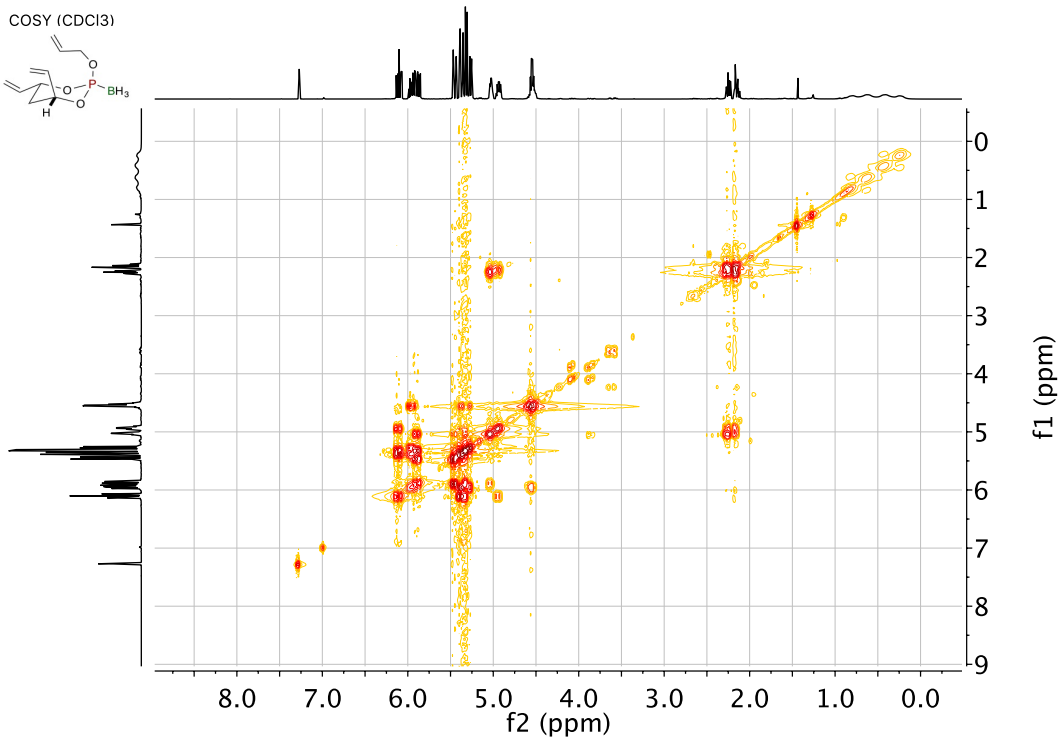


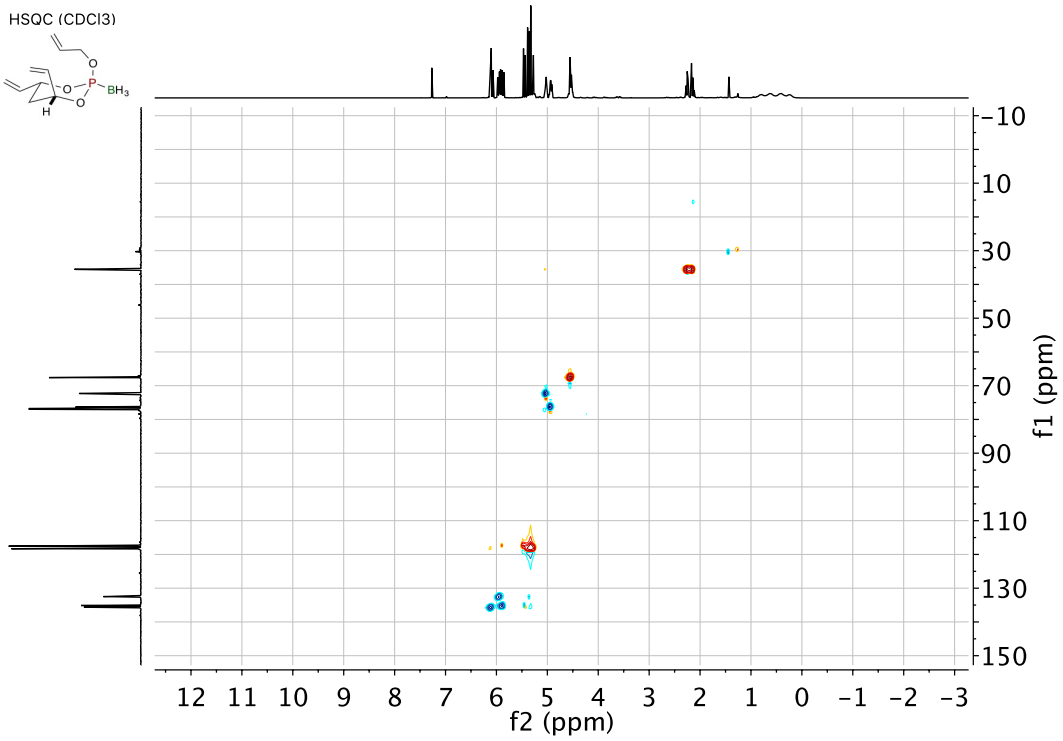

3.9.3

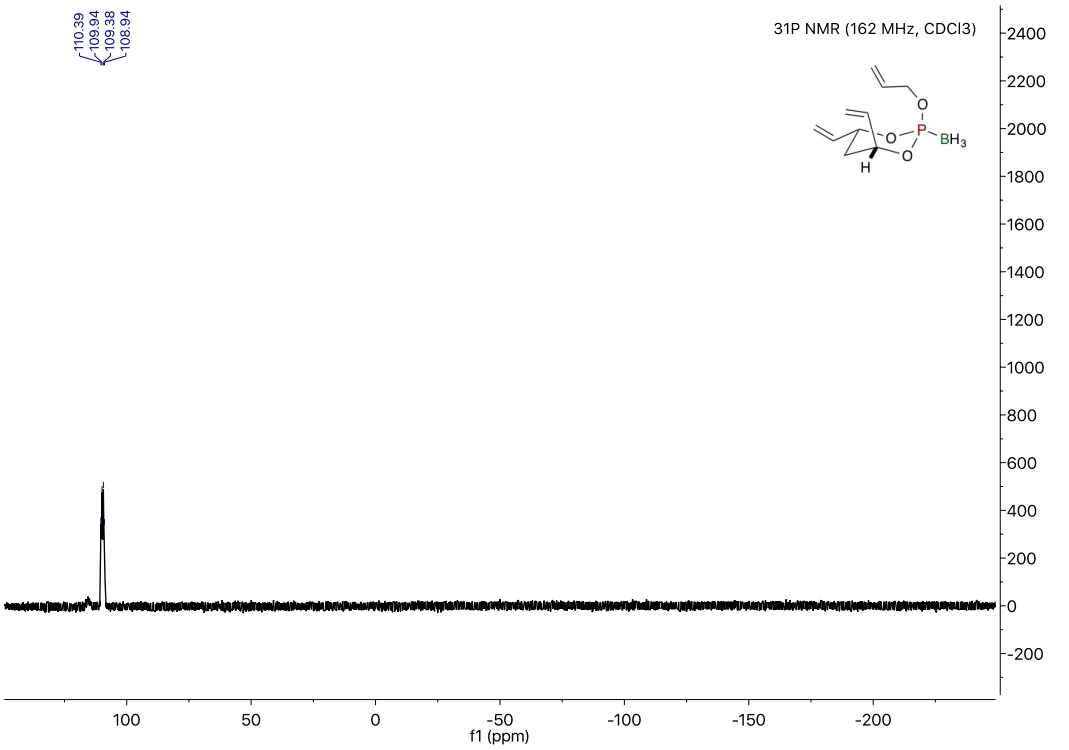


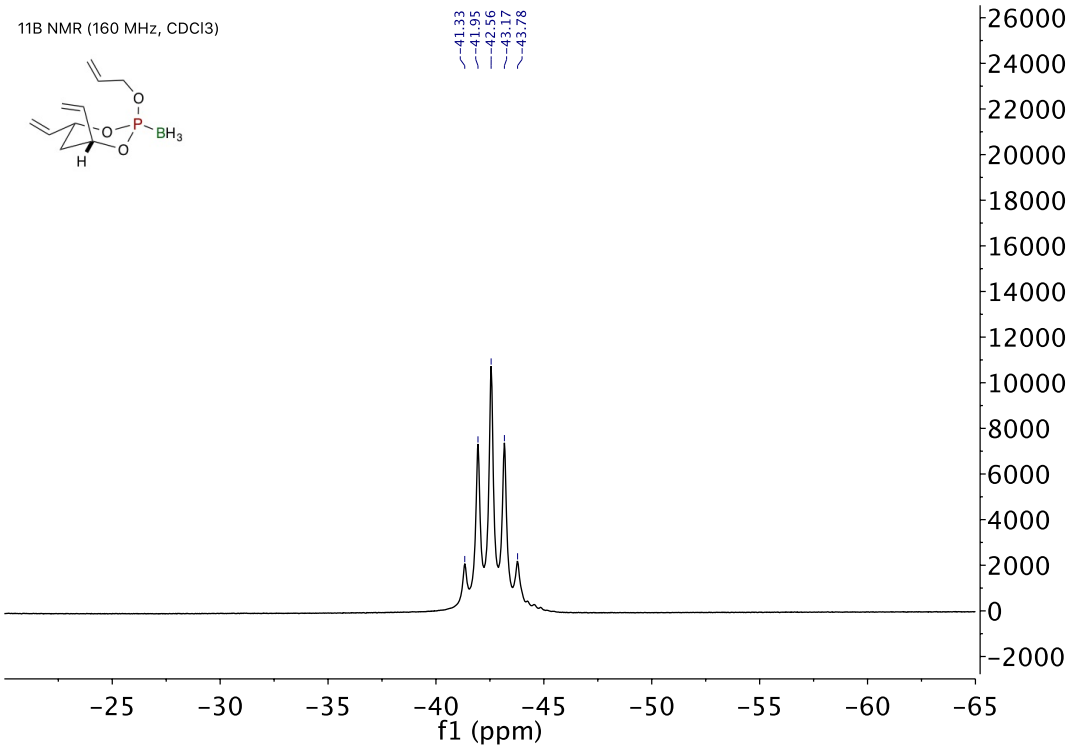

13C NMR (126 MHz, CDCl3)
135.65
135.63
135.18
135.13
132.54
132.49
118.31
118.15
117.56
117.56
77.25
77.00
76.75
76.30
76.23
72.34
72.28
67.60
35.56
35.49
O
P
BH3
O
O
H
280000
260000
240000
220000
200000
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
-20000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)


13C NMR {1H} (126 MHz, CDCl3)
135.70
135.69
135.23
135.18
132.59
132.54
118.36
118.20
117.62
76.36
76.28
72.40
72.33
67.65
35.55
O
P
BH3
O
O
H
150000
130000
110000
90000
70000
50000
30000
10000
-10000
-30000
-50000
-70000
-90000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

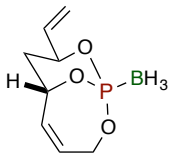

COSY (CDCl3)
f2 (ppm)
f1 (ppm)


HSQC (CDCl3)
f2 (ppm)
f1 (ppm)

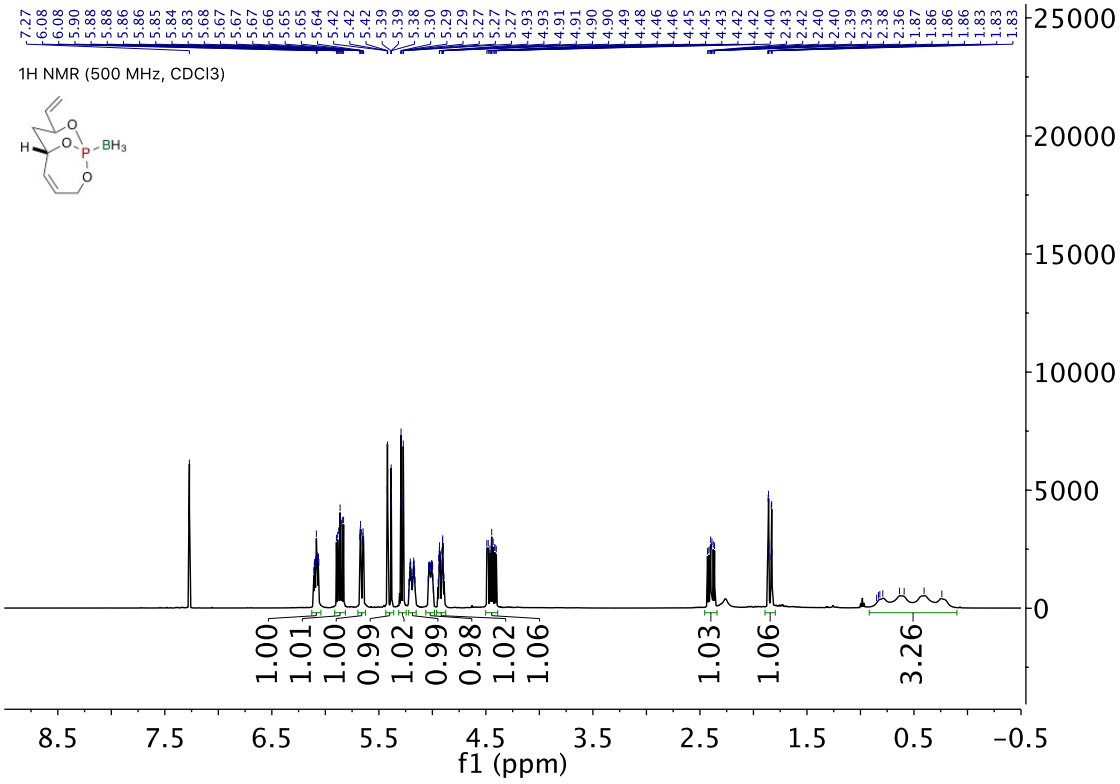

110.39
109.94
109.38
108.94
31P NMR (162 MHz, CDCl3)
O
P
BH3
O
O
H
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
100
50
0
-50
-100
-150
-200
f1 (ppm)

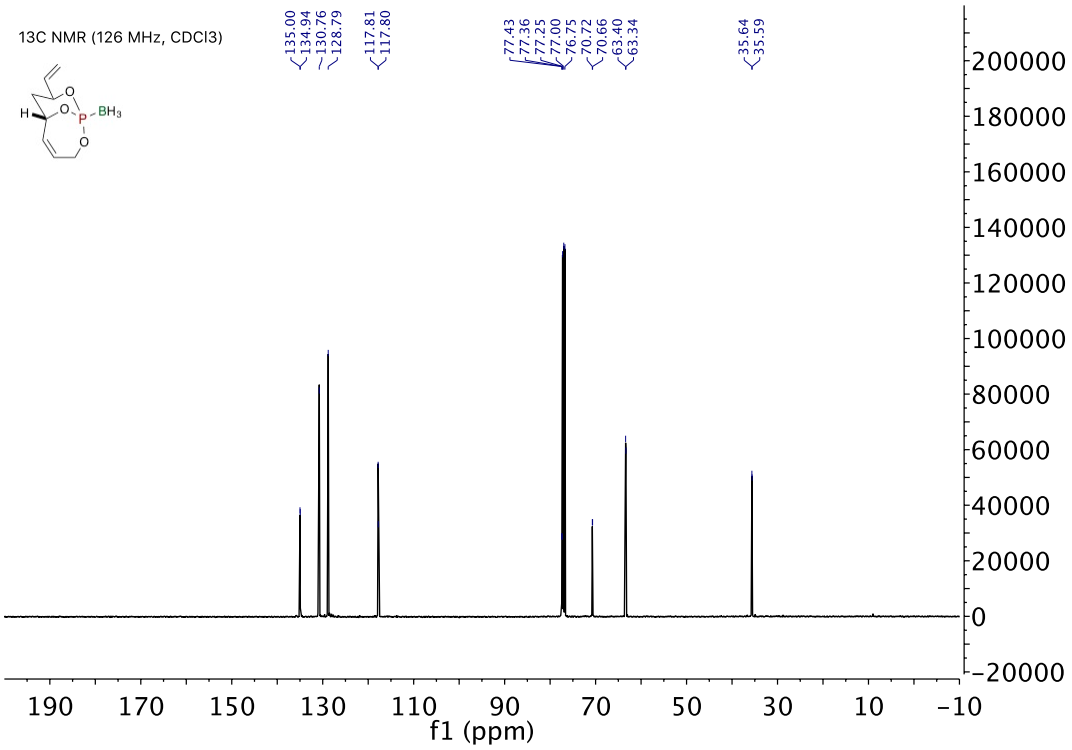

11B NMR (160 MHz, CDCl3)
-41.33
-41.95
-42.56
-43.17
-43.78
O
P
BH3
O
O
H
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
-25
-30
-35
-40
-45
-50
-55
-60
-65
f1 (ppm)

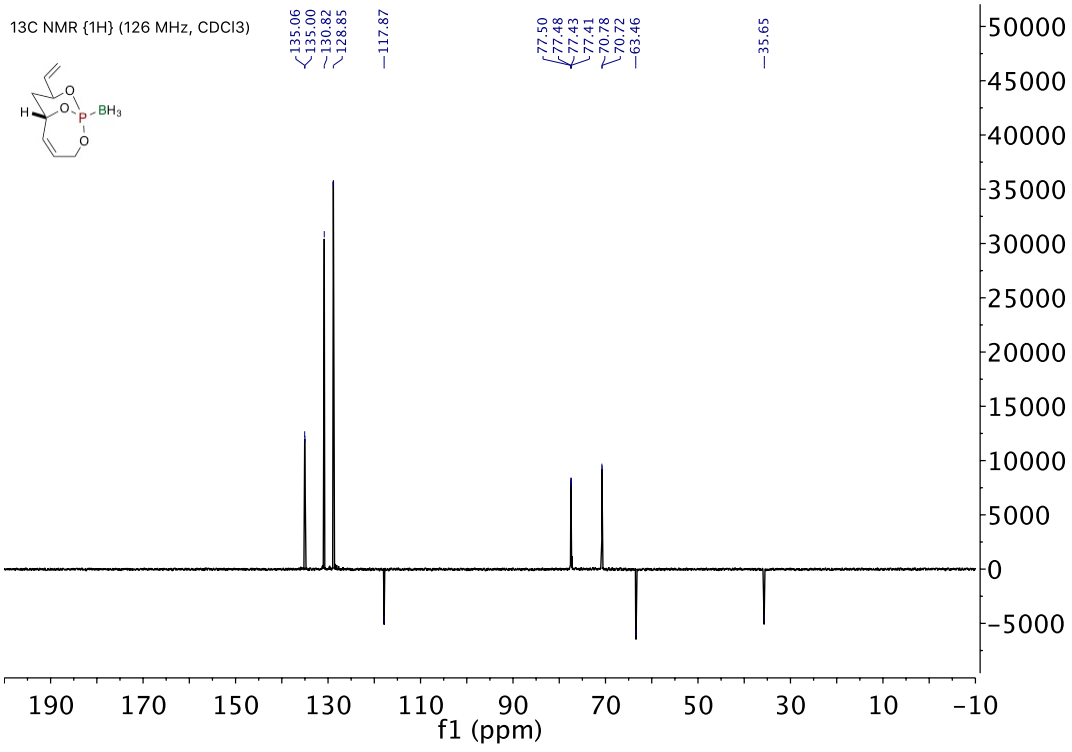
**(1*S*,6*S*,8*S*)-8-vinyl-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-borane ($C_8H_{14}BO_3P$, 3.9.4)**

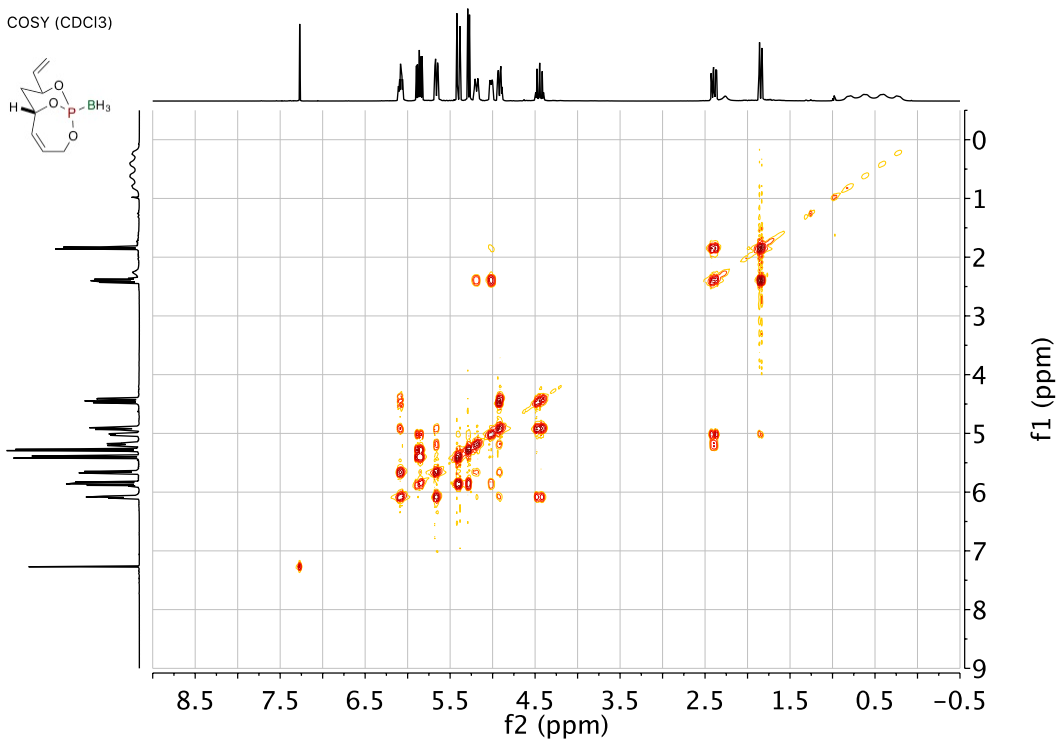


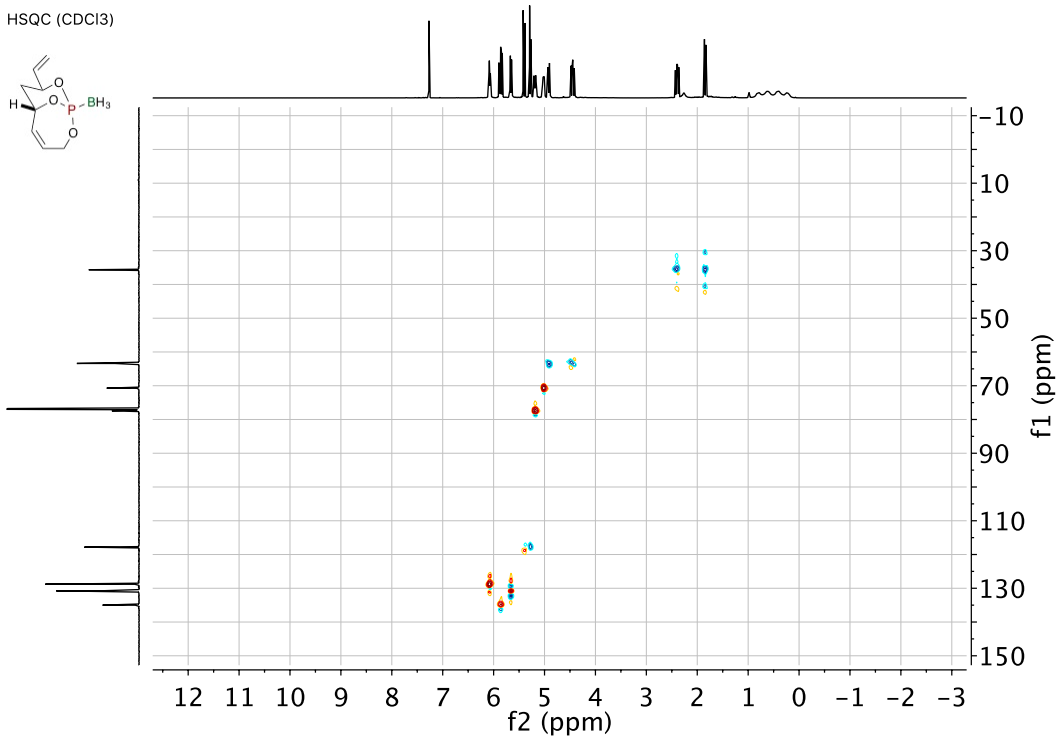
($S_P$,*S*,*S*)-**3.9.4**

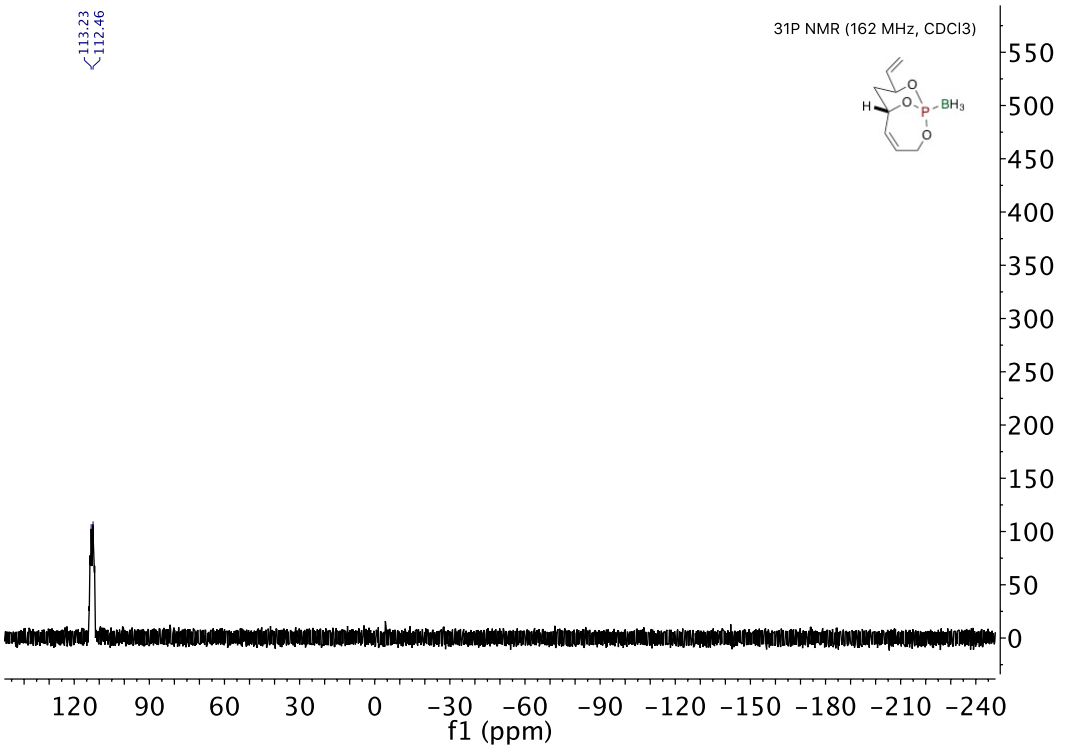


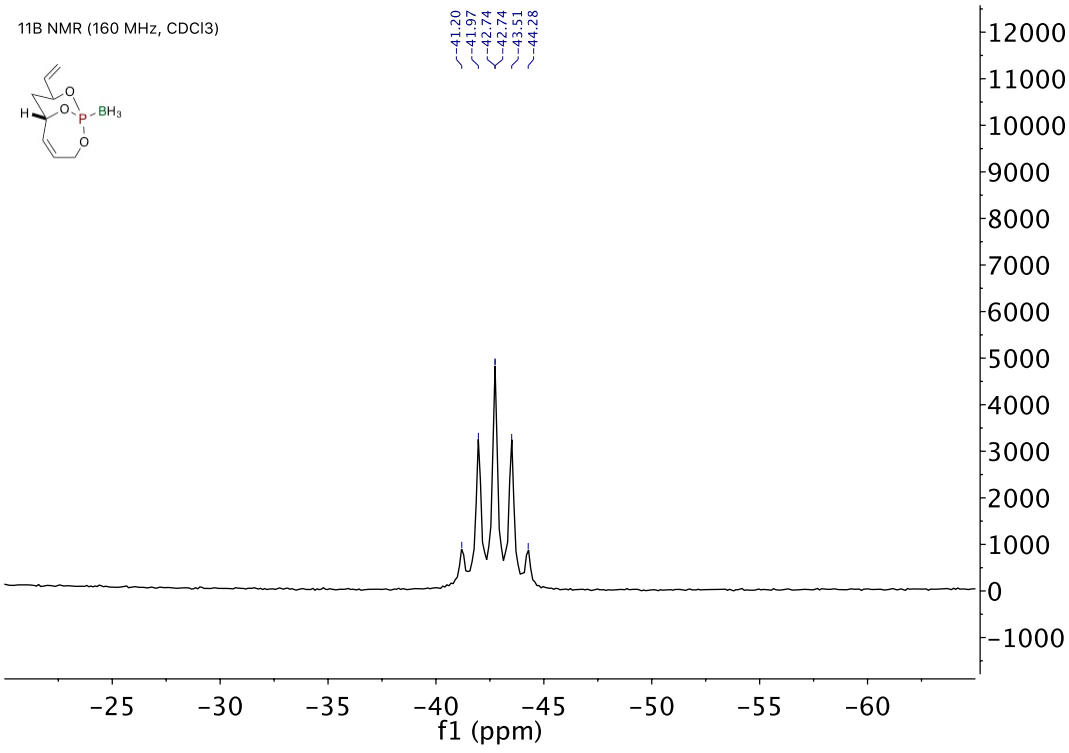

13C NMR (126 MHz, CDCl3)
135.00
134.94
130.76
128.79
117.81
117.80
77.43
77.36
77.25
77.00
76.75
70.72
70.66
63.40
63.34
35.64
35.59
200000
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
-20000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)


13C NMR {1H} (126 MHz, CDCl3)
135.06
135.00
130.82
128.85
117.87
77.50
77.48
77.43
77.41
70.78
70.72
63.46
35.65
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

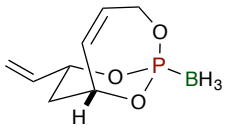

COSY (CDCl3)
BH3
f2 (ppm)
f1 (ppm)


HSQC (CDCl3)
BH3
f2 (ppm)
f1 (ppm)

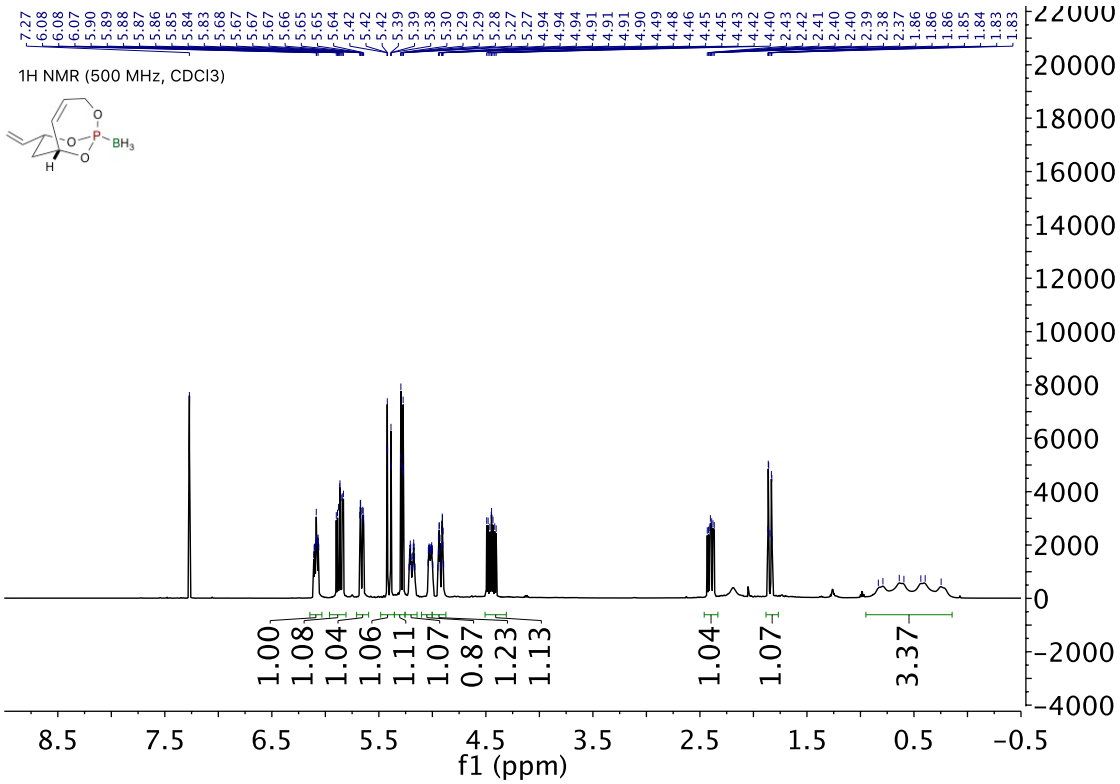

113.23
112.46
31P NMR (162 MHz, CDCl3)
550
500
450
400
350
300
250
200
150
100
50
0
120 90 60 30 0 -30 -60 -90 -120 -150 -180 -210 -240
f1 (ppm)

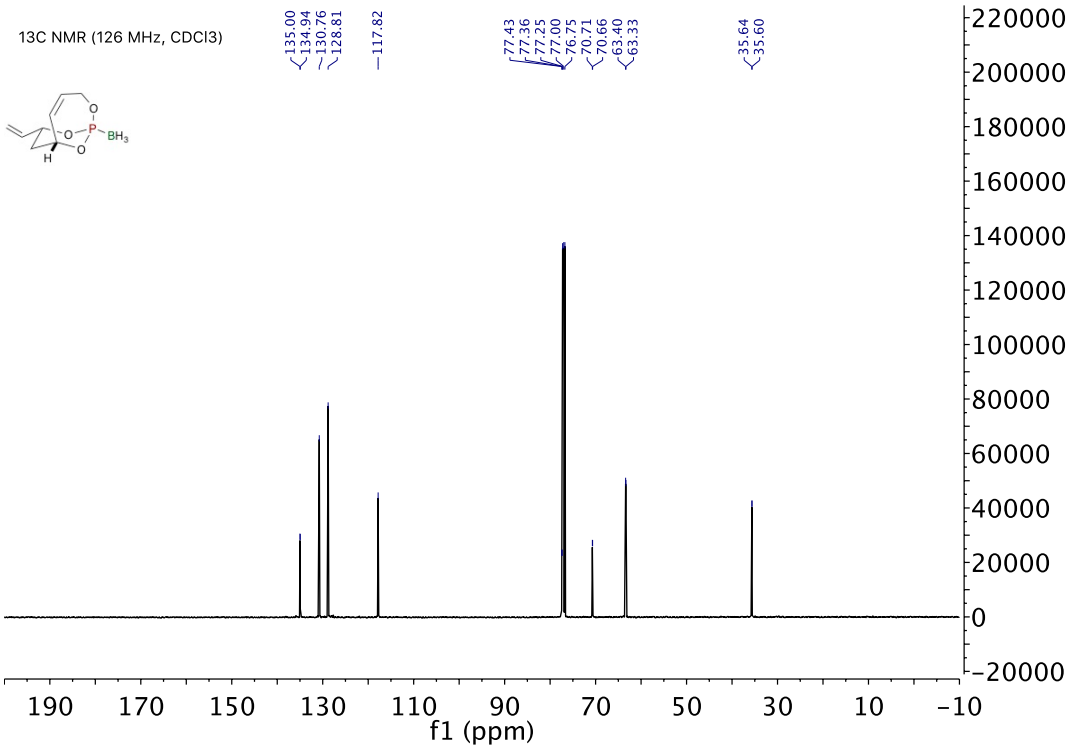

11B NMR (160 MHz, CDCl3)
-41.20
-41.97
-42.74
-42.74
-43.51
-44.28
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-25 -30 -35 -40 -45 -50 -55 -60
f1 (ppm)

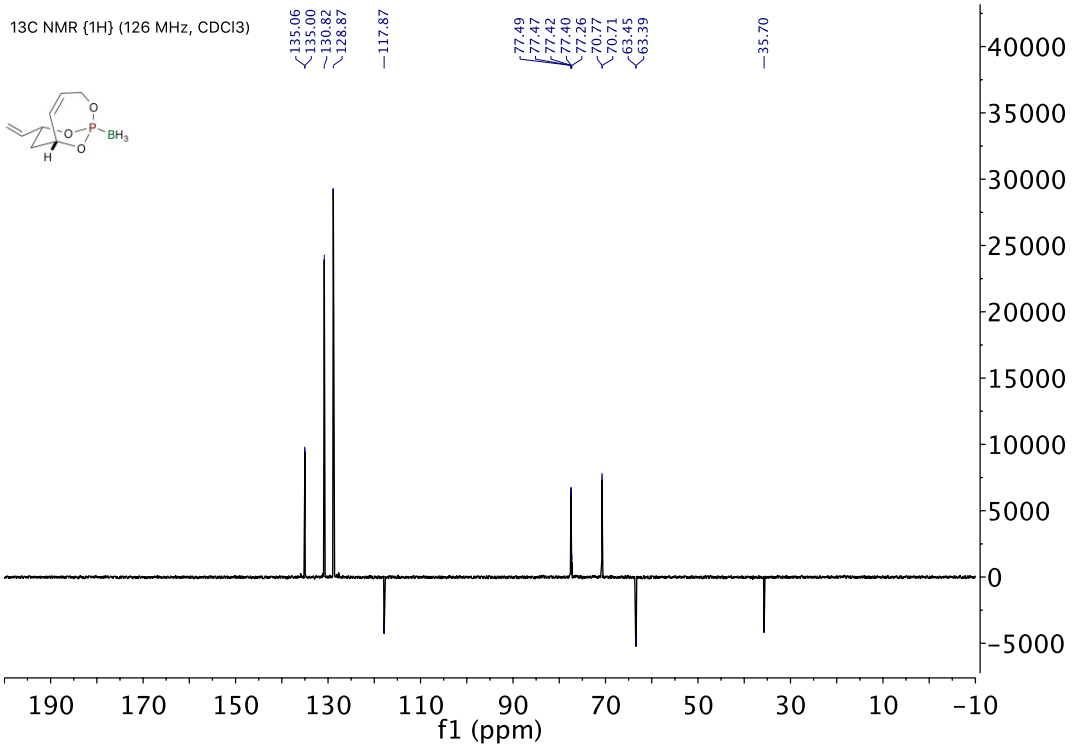
**(1*R*,6*R*,8*R*)-8-vinyl-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-borane ($C_8H_{14}BO_3P$, 3.9.5)**

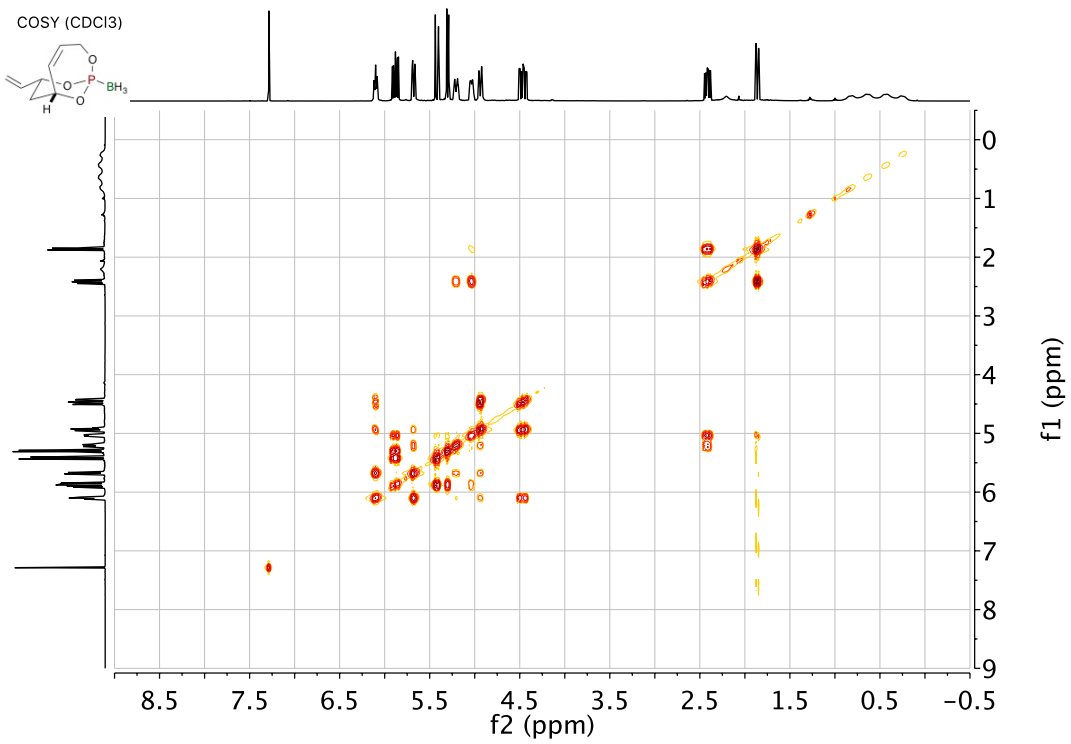


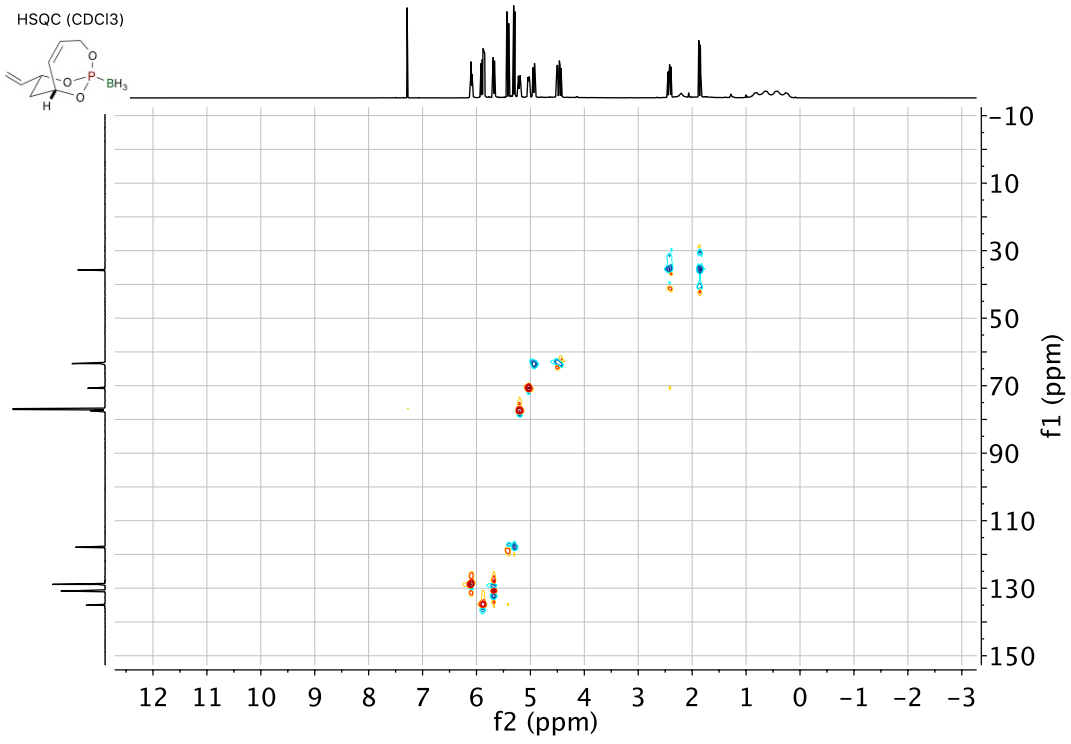
($R_P$,*R*,*R*)-**3.9.5**

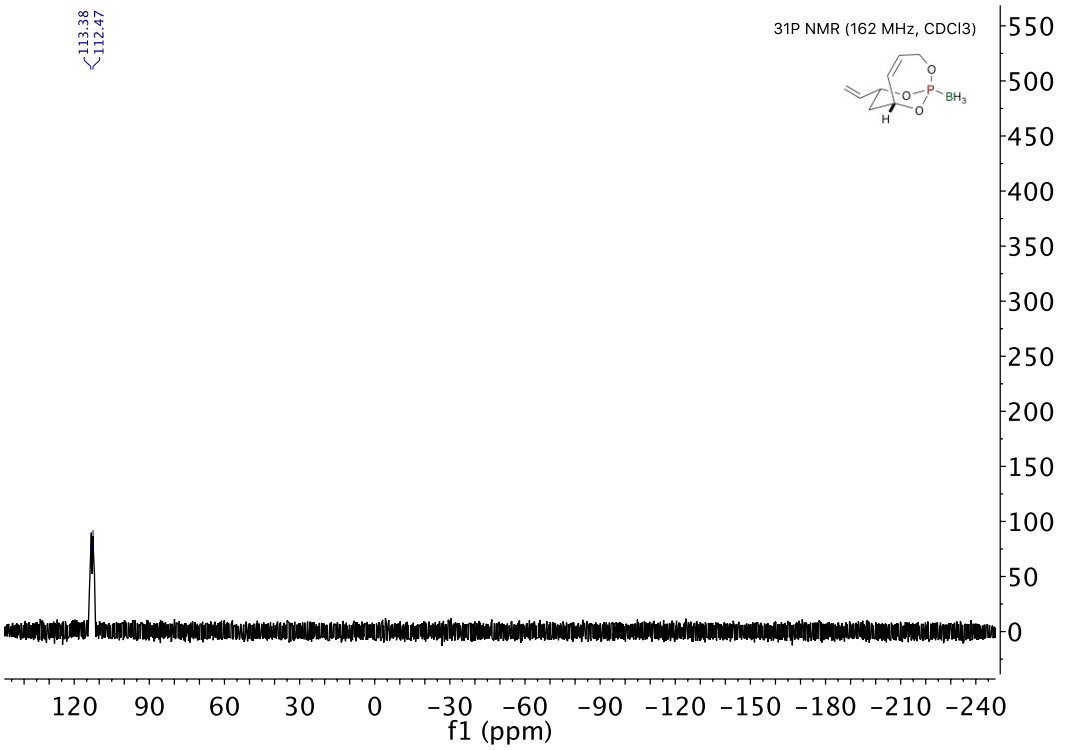


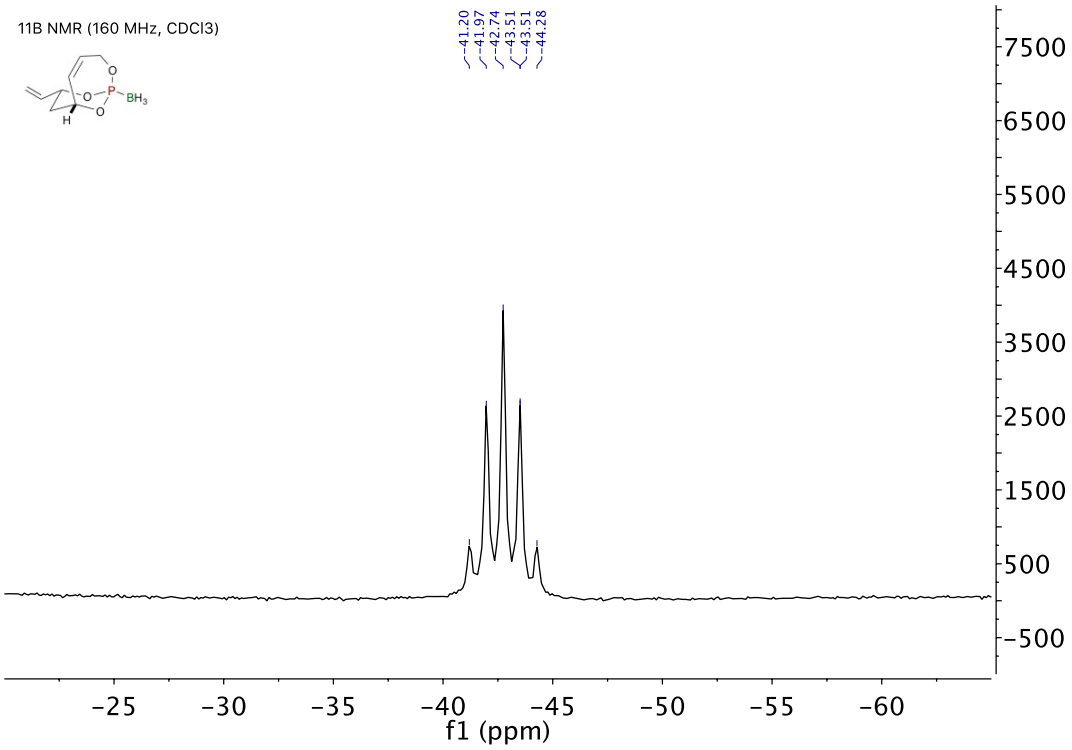

13C NMR (126 MHz, CDCl3)
135.00
134.94
130.76
128.81
117.82
77.43
77.36
77.25
77.00
76.75
70.71
70.66
63.40
63.33
35.64
35.60
220000
200000
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
-20000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)


13C NMR {1H} (126 MHz, CDCl3)
135.06
135.00
130.82
128.87
117.87
77.49
77.47
77.42
77.40
77.26
70.77
70.71
63.45
63.39
35.70
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

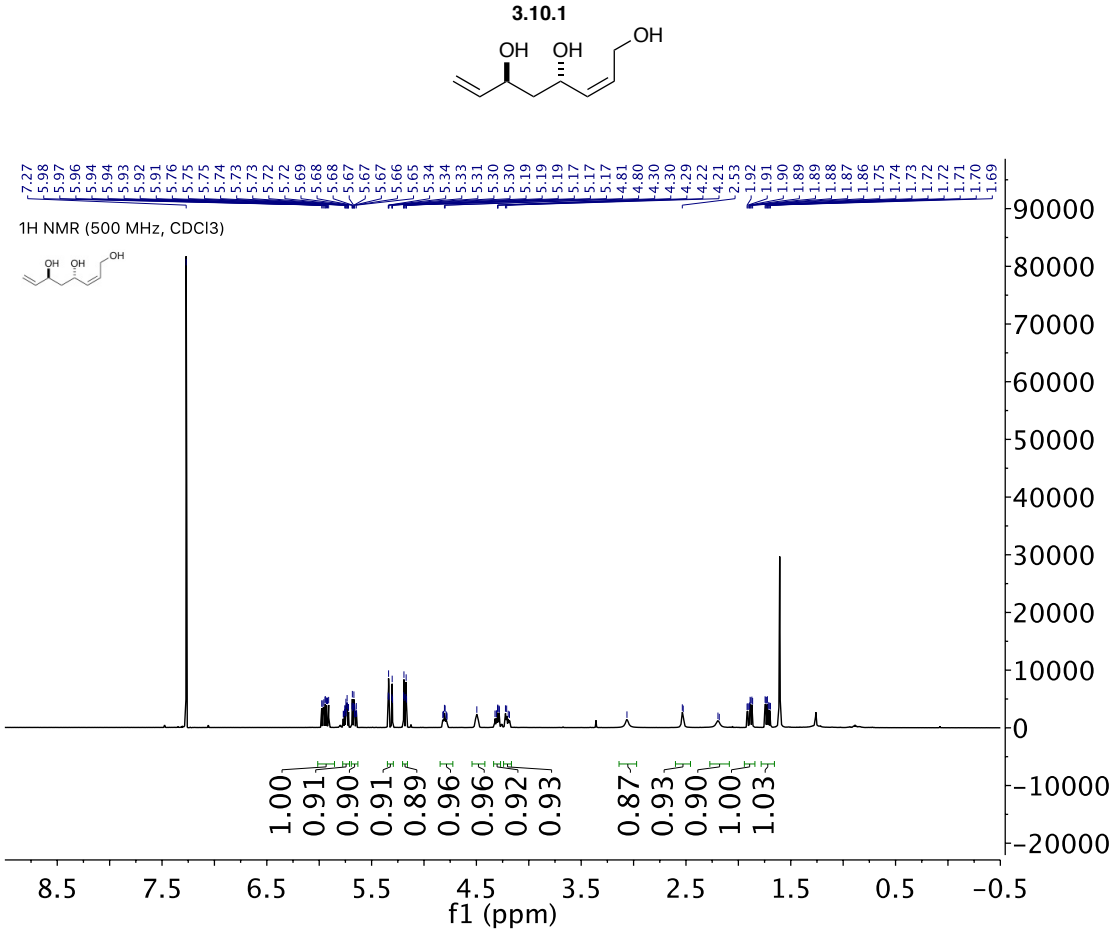

COSY (CDCl3)
f2 (ppm)
f1 (ppm)

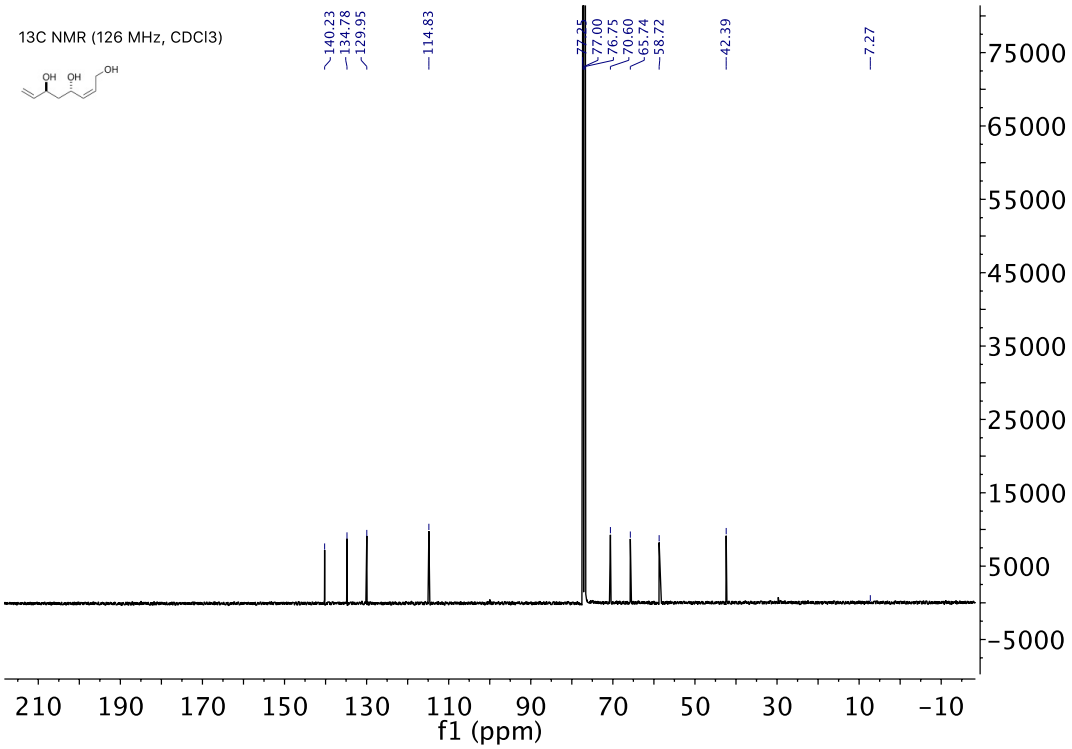

HSQC (CDCl3)
f2 (ppm)
f1 (ppm)


31P NMR (162 MHz, CDCl3)
113.38
112.47
550
500
450
400
350
300
250
200
150
100
50
0
120 90 60 30 0 -30 -60 -90 -120 -150 -180 -210 -240
f1 (ppm)

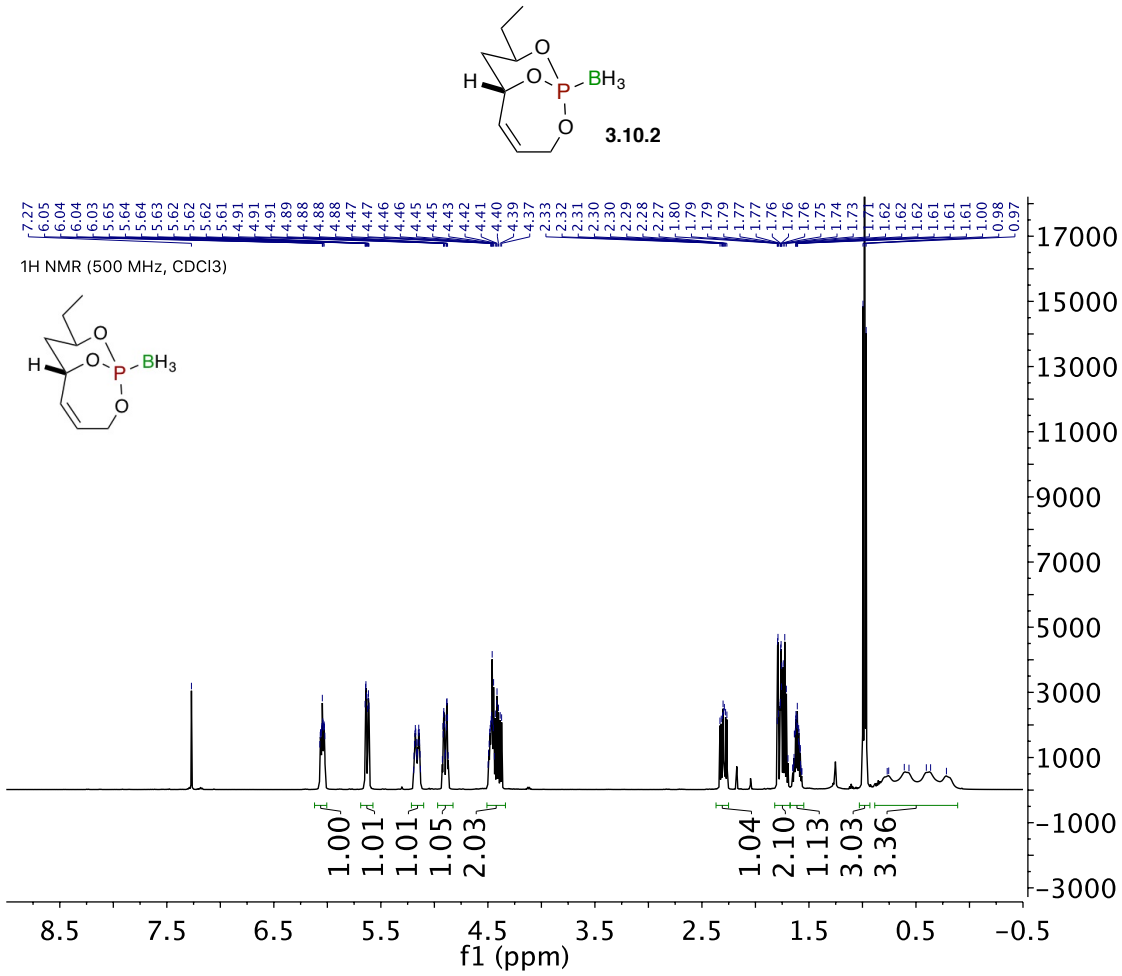

11B NMR (160 MHz, CDCl3)
-41.20
-41.97
-42.74
-43.51
-43.51
-44.28
7500
6500
5500
4500
3500
2500
1500
500
-500
-25 -30 -35 -40 -45 -50 -55 -60
f1 (ppm)

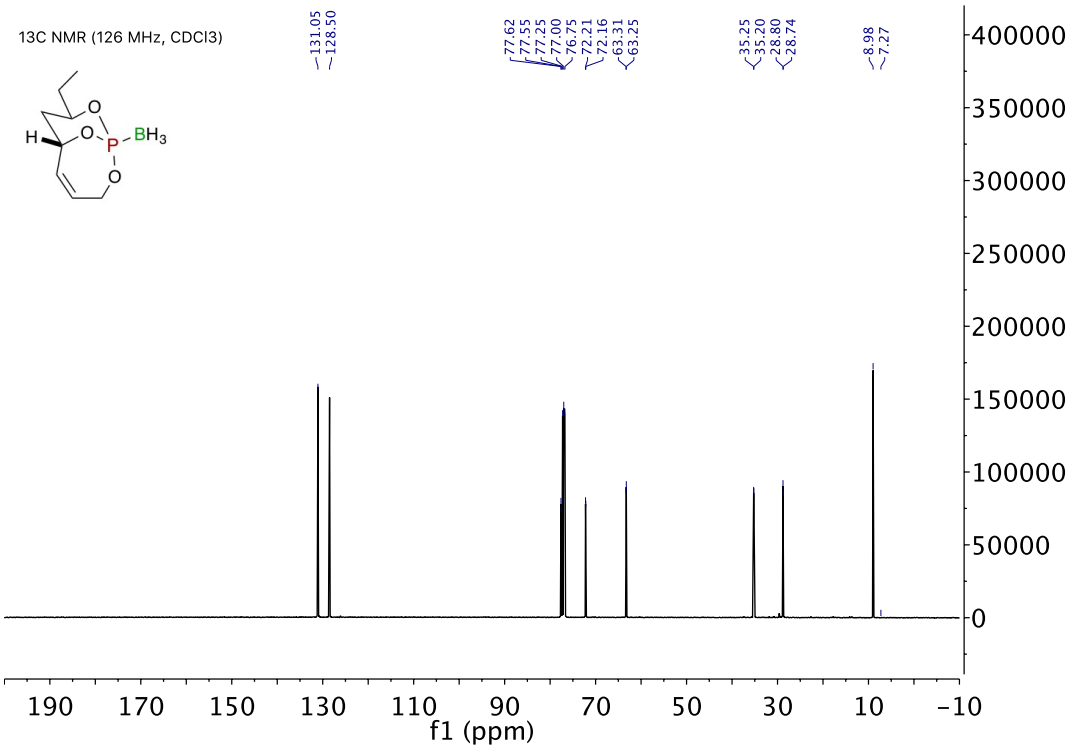
**(4*S*,6*S*,*Z*)-octa-2,7-diene-1,4,6-triol ($C_8H_{14}O_3$, 3.10.1)**

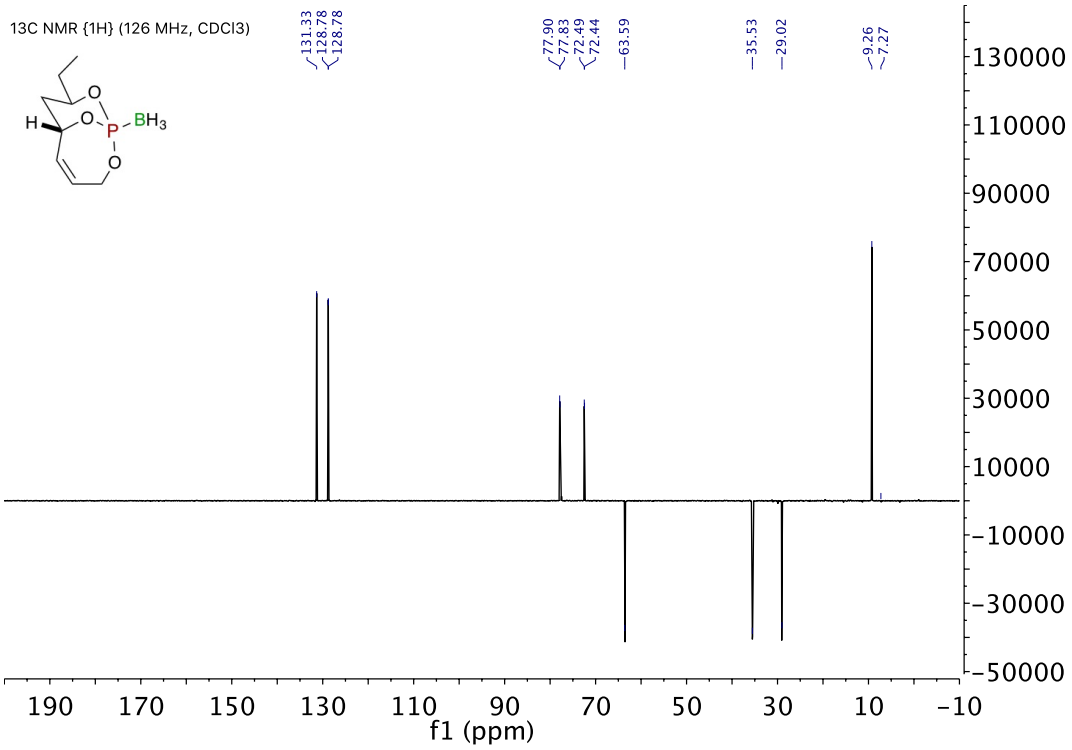


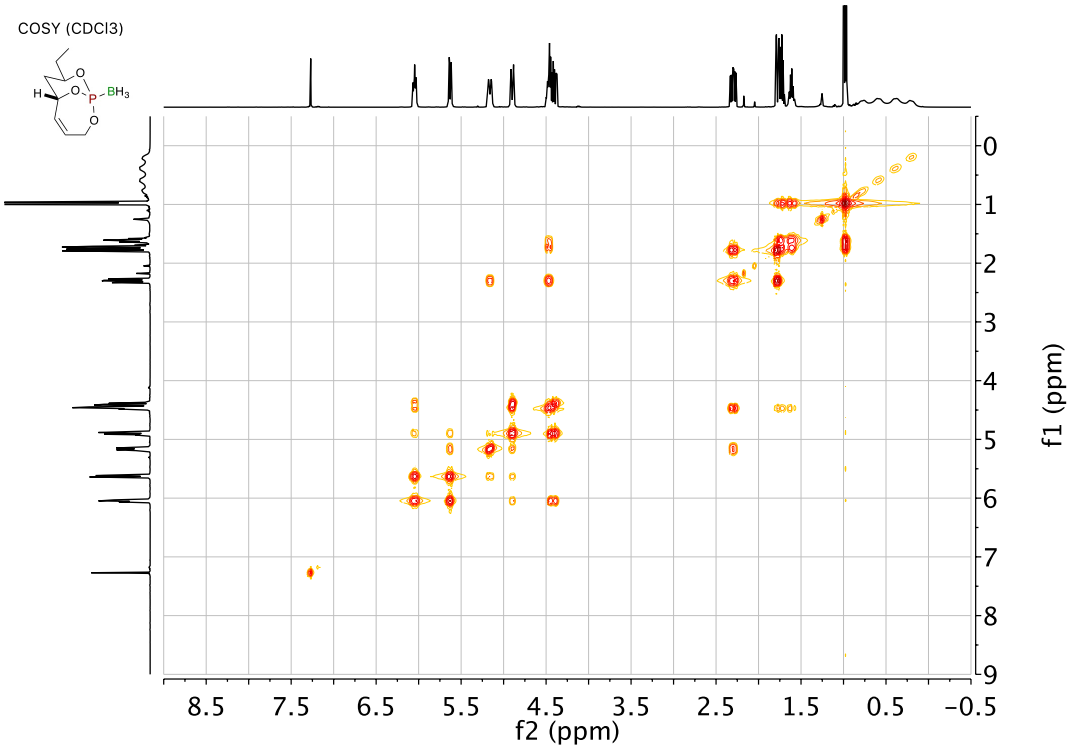

13C NMR (126 MHz, CDCl3)
OH
OH
OH
140.23
134.78
129.95
114.83
77.25
77.00
76.75
70.60
65.74
58.72
42.39
7.27
75000
65000
55000
45000
35000
25000
15000
5000
-5000
210
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

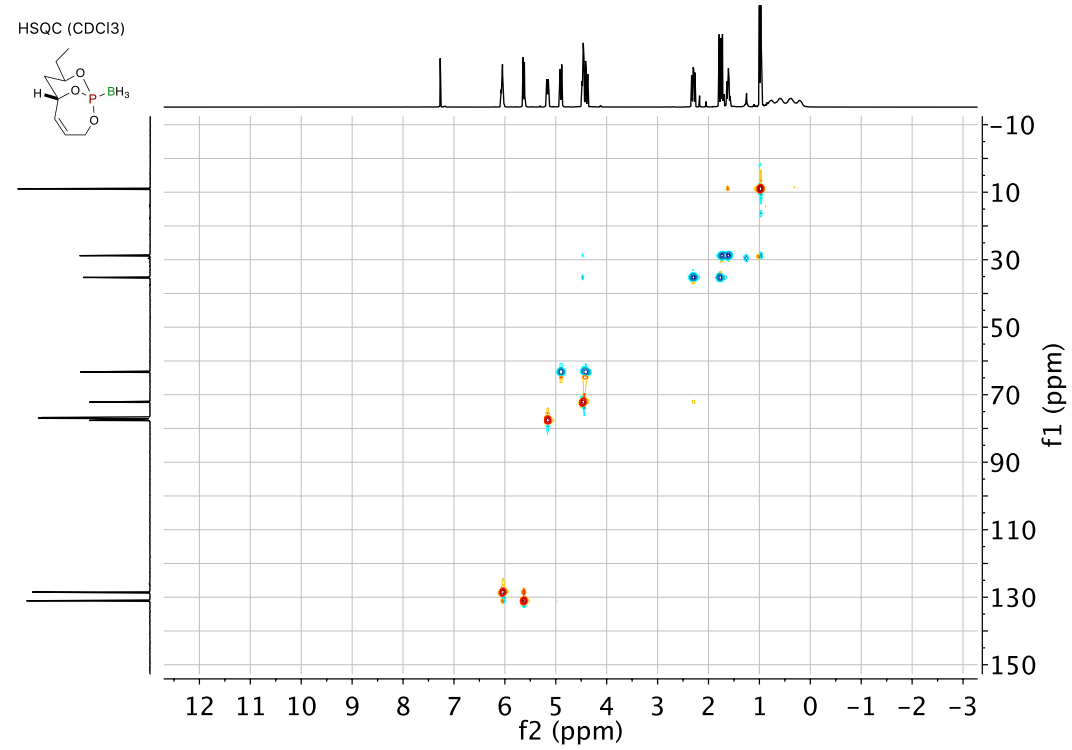
**(1*S*,6*S*,8*R*)-8-ethyl-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-borane ($C_8H_{16}BO_3P$, 3.10.2)**

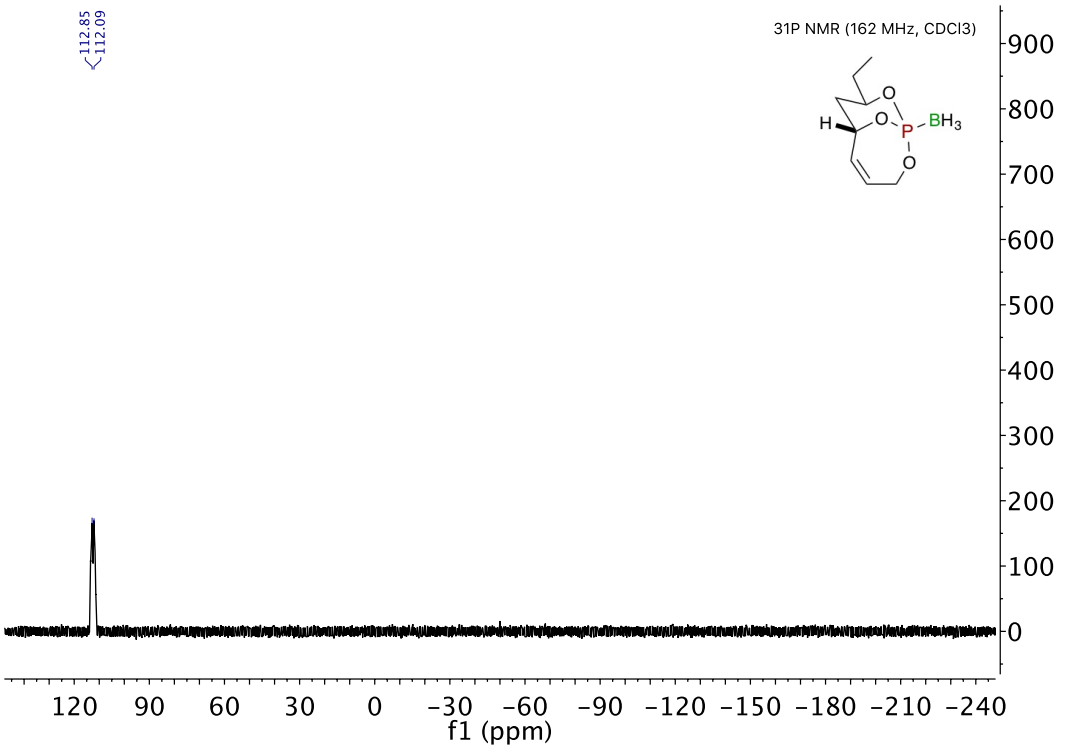


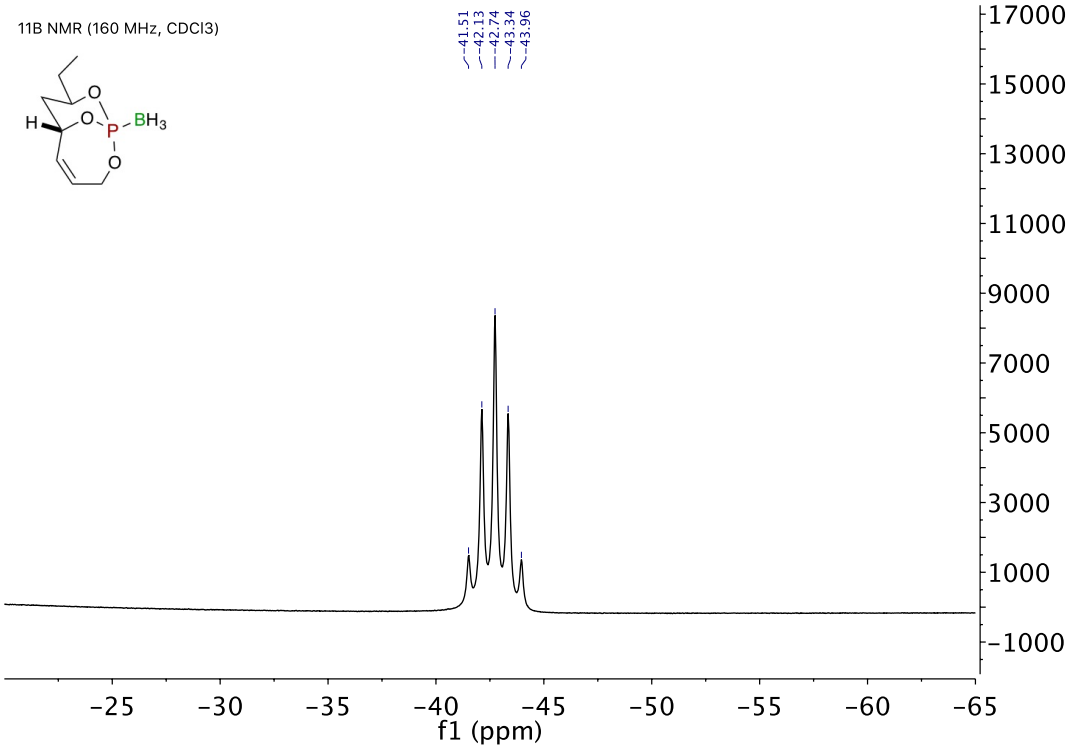

13C NMR (126 MHz, CDCl3)
131.05
128.50
77.62
77.55
77.25
77.00
76.75
72.21
72.16
63.31
63.25
35.25
35.20
28.80
28.74
8.98
7.27
400000
350000
300000
250000
200000
150000
100000
50000
0
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)


13C NMR {1H} (126 MHz, CDCl3)
131.33
128.78
128.78
77.90
77.83
72.49
72.44
63.59
35.53
29.02
9.26
7.27
130000
110000
90000
70000
50000
30000
10000
-10000
-30000
-50000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

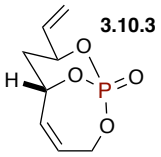

COSY (CDCl3)
f2 (ppm)
f1 (ppm)

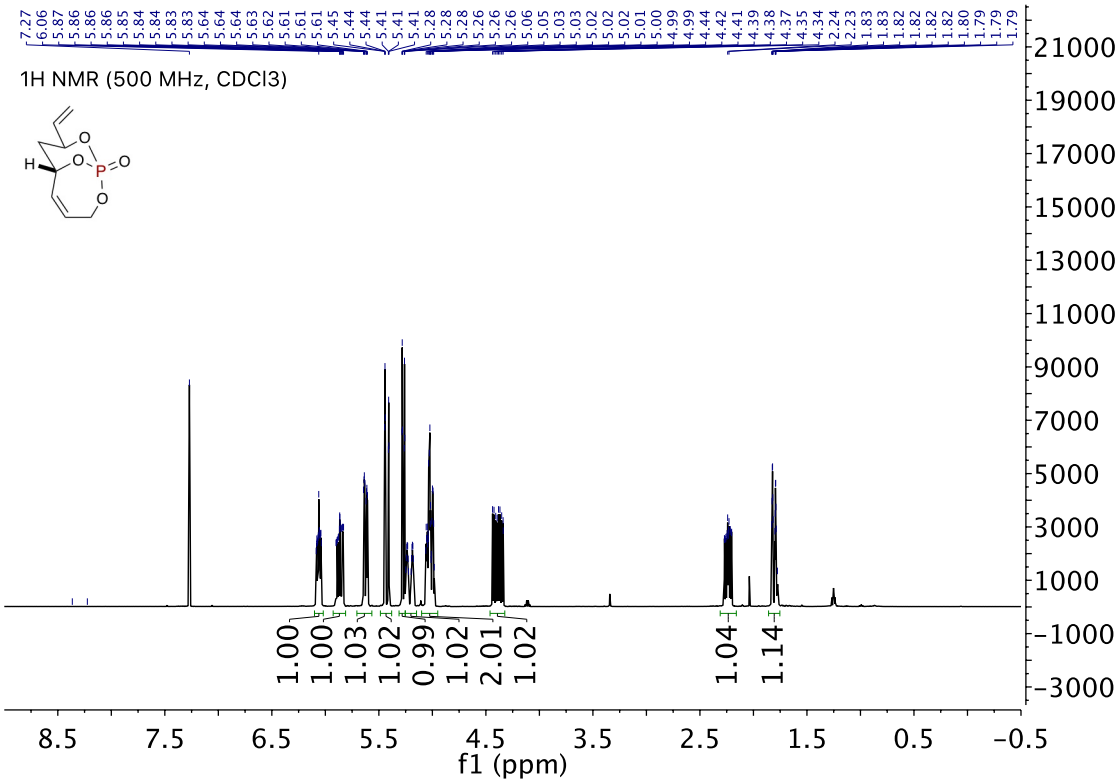

HSQC (CDCl3)
f2 (ppm)
f1 (ppm)

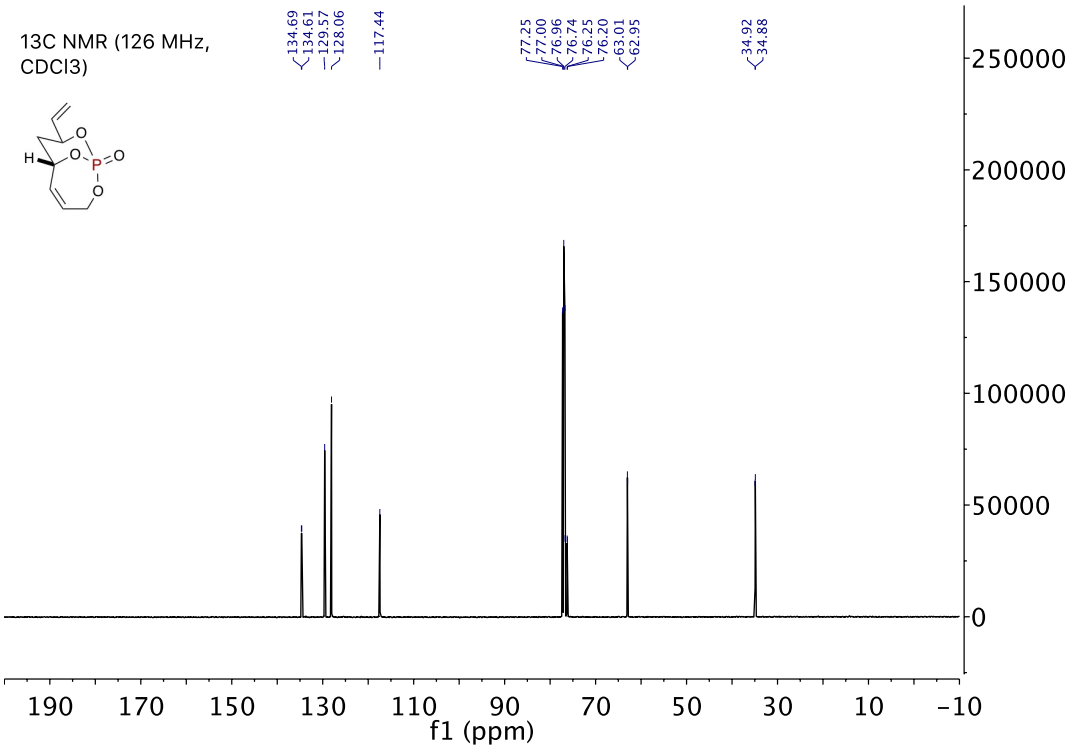

112.85
112.09
31P NMR (162 MHz, CDCl3)
O
O
P
BH3
H
O
900
800
700
600
500
400
300
200
100
0
120
90
60
30
0
-30
-60
-90
-120
-150
-180
-210
-240
f1 (ppm)

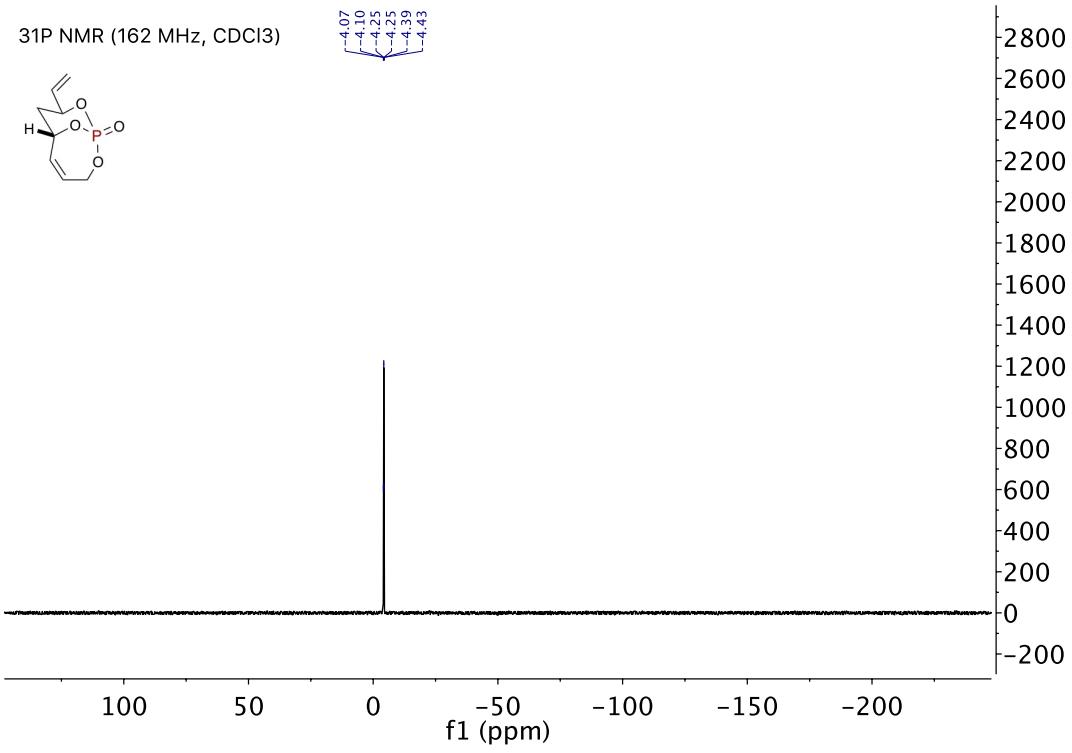

11B NMR (160 MHz, CDCl3)
-41.51
-42.13
-42.74
-43.34
-43.96
O
O
P
BH3
H
O
17000
15000
13000
11000
9000
7000
5000
3000
1000
-1000
-25
-30
-35
-40
-45
-50
-55
-60
-65
f1 (ppm)

**(1*S*,6*S*,8*S*)-8-vinyl-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-oxide ($C_8H_{11}O_4P$, 3.10.3)**

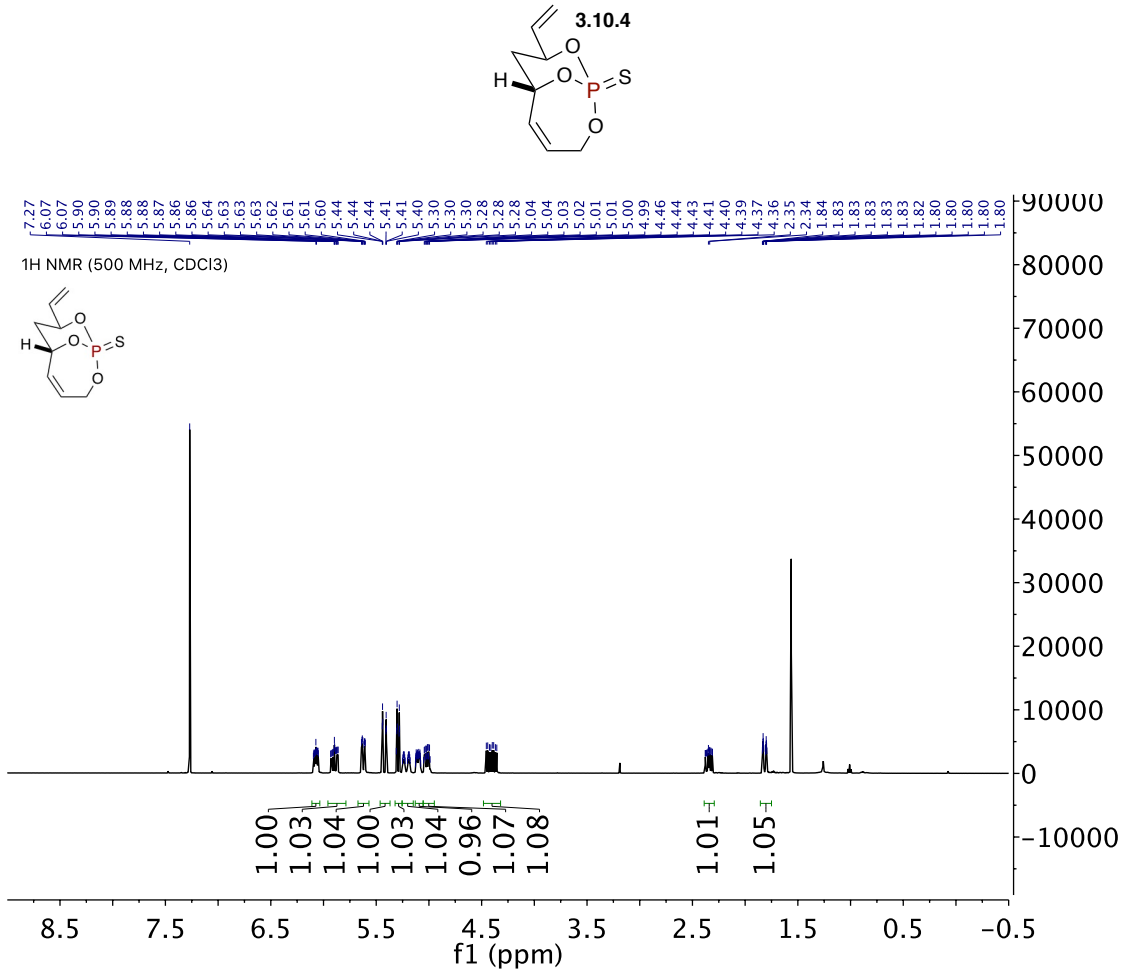


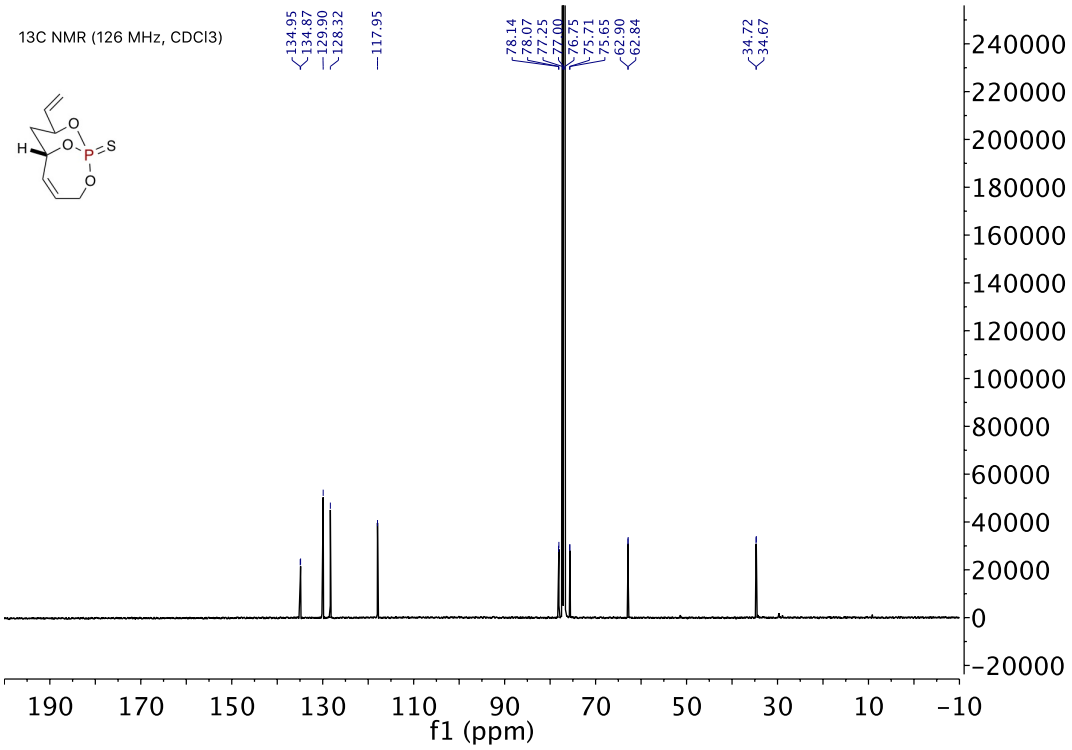



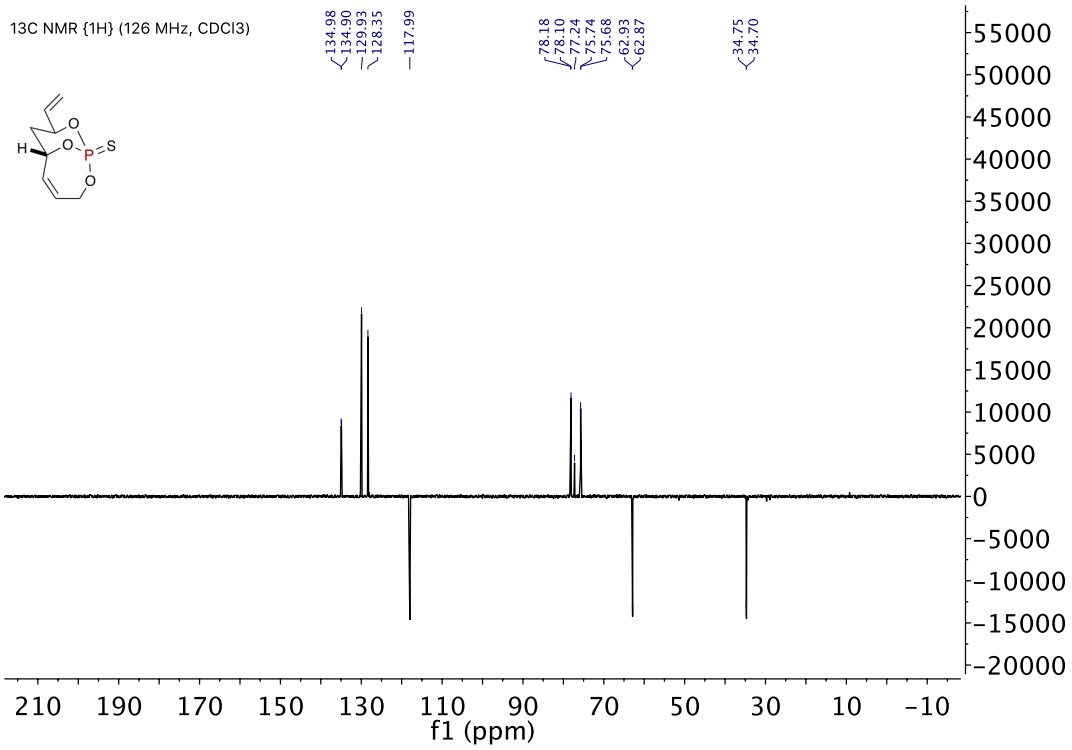

13C NMR (126 MHz, CDCl3)
134.69
134.61
129.57
128.06
117.44
77.25
77.00
76.96
76.74
76.25
76.20
63.01
62.95
34.92
34.88
250000
200000
150000
100000
50000
0
190
170
150
130
110
90
70
50
30
10
−10
f1 (ppm)

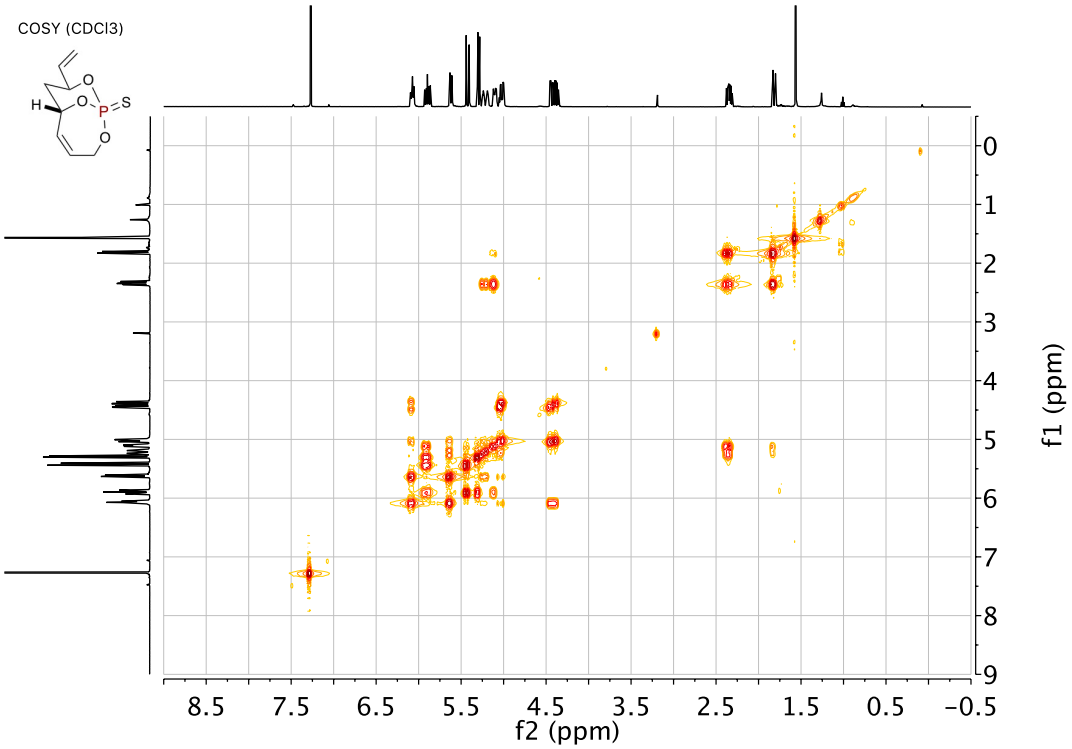

31P NMR (162 MHz, CDCl3)
4.07
4.10
4.25
4.25
4.39
4.43
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
−200
100
50
0
−50
−100
−150
−200
f1 (ppm)

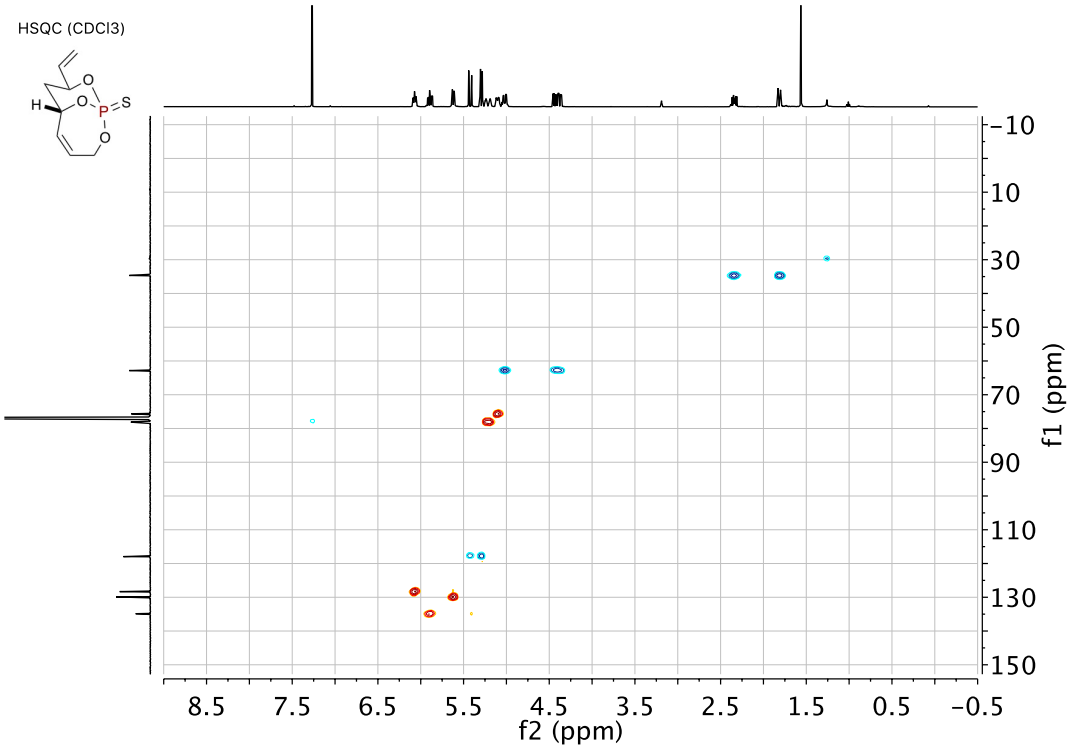
**(1*R*,6*S*,8*S*)-8-vinyl-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-sulfide ($C_8H_{11}O_3PS$, 3.10.4)**

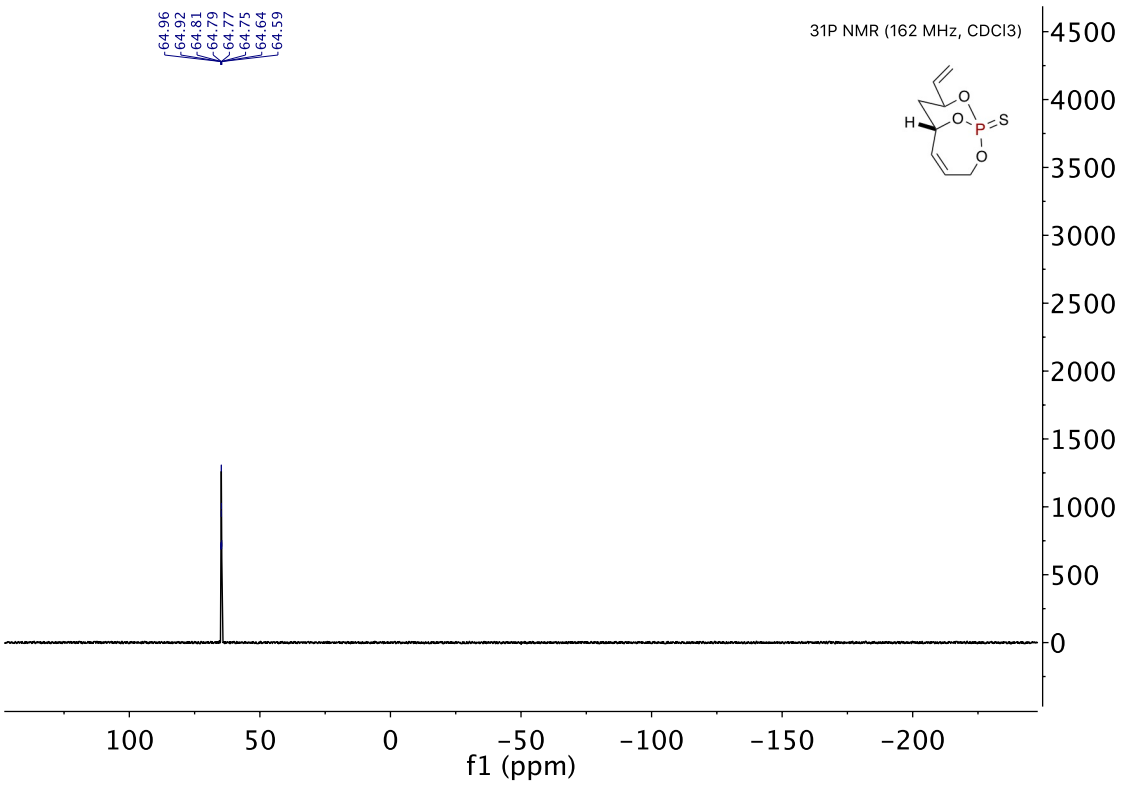



13C NMR (126 MHz, CDCl3)
134.95
134.87
129.90
128.32
117.95
78.14
78.07
77.25
77.00
76.75
75.71
75.65
62.90
62.84
34.72
34.67
240000
220000
200000
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
-20000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

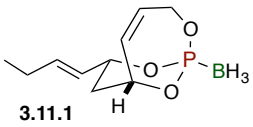

13C NMR {1H} (126 MHz, CDCl3)
134.98
134.90
129.93
128.35
117.99
78.18
78.10
77.24
75.74
75.68
62.93
62.87
34.75
34.70
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
-10000
-15000
-20000
210
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)


COSY (CDCl3)
f2 (ppm)
f1 (ppm)

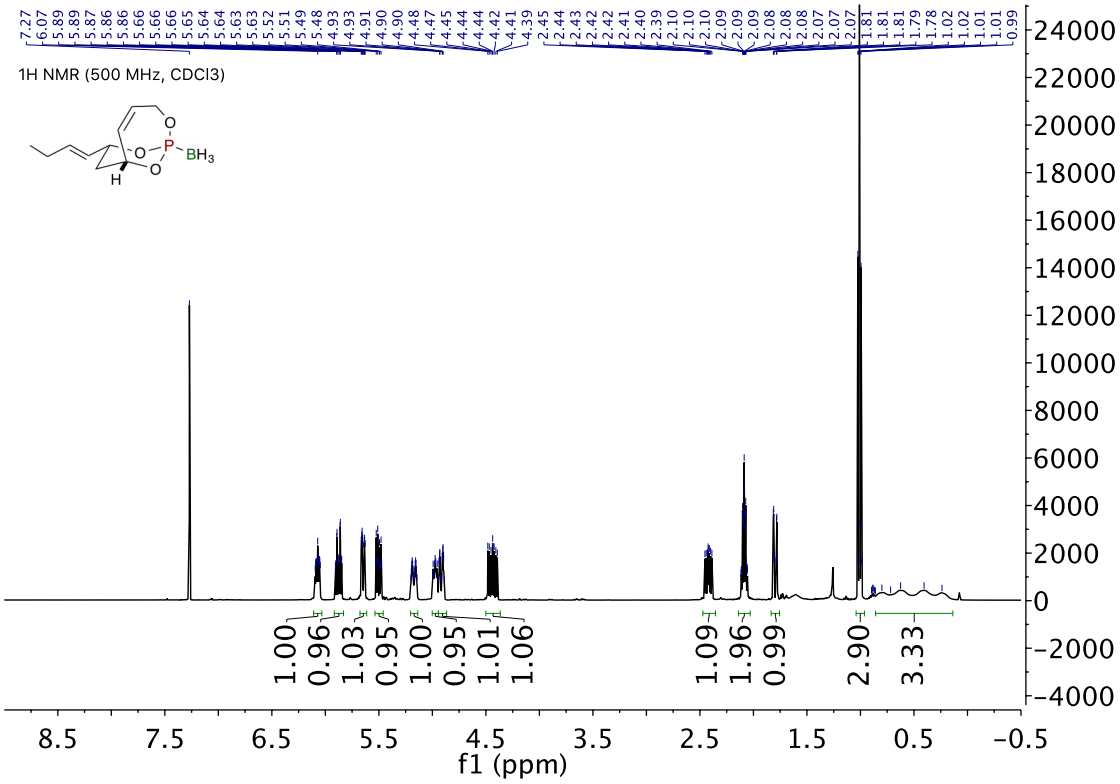

HSQC (CDCl3)
f2 (ppm)
f1 (ppm)

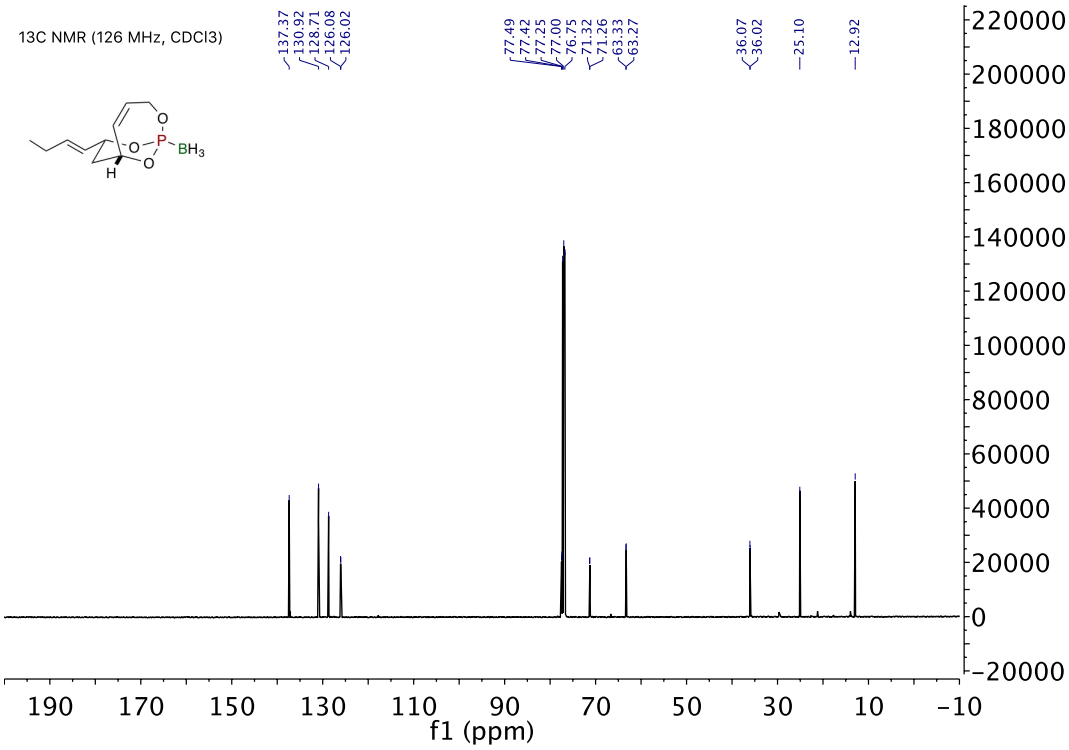

64.96
64.92
64.81
64.79
64.77
64.75
64.64
64.59
31P NMR (162 MHz, CDCl3)
4500
4000
3500
3000
2500
2000
1500
1000
500
0
100
50
0
−50
−100
−150
−200
f1 (ppm)

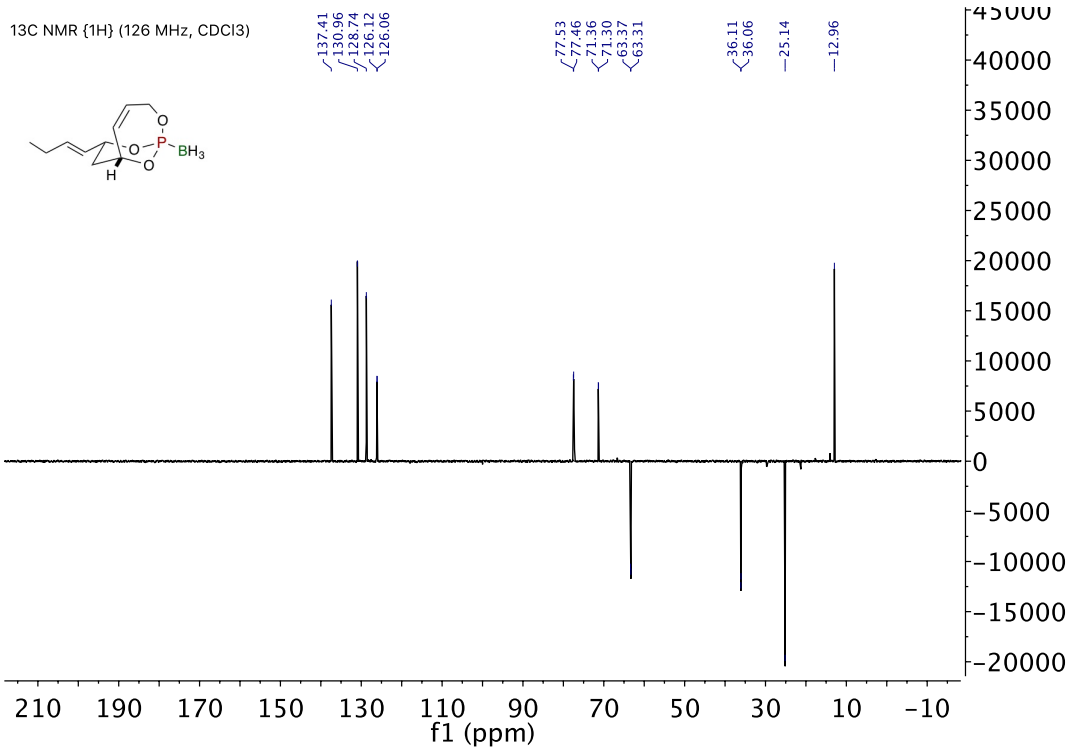
**(1*R*,6*R*,8*R*)-8-((*E*)-but-1-en-1-yl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-borane ($C_{10}H_{18}BO_3P$, 3.11.1)**

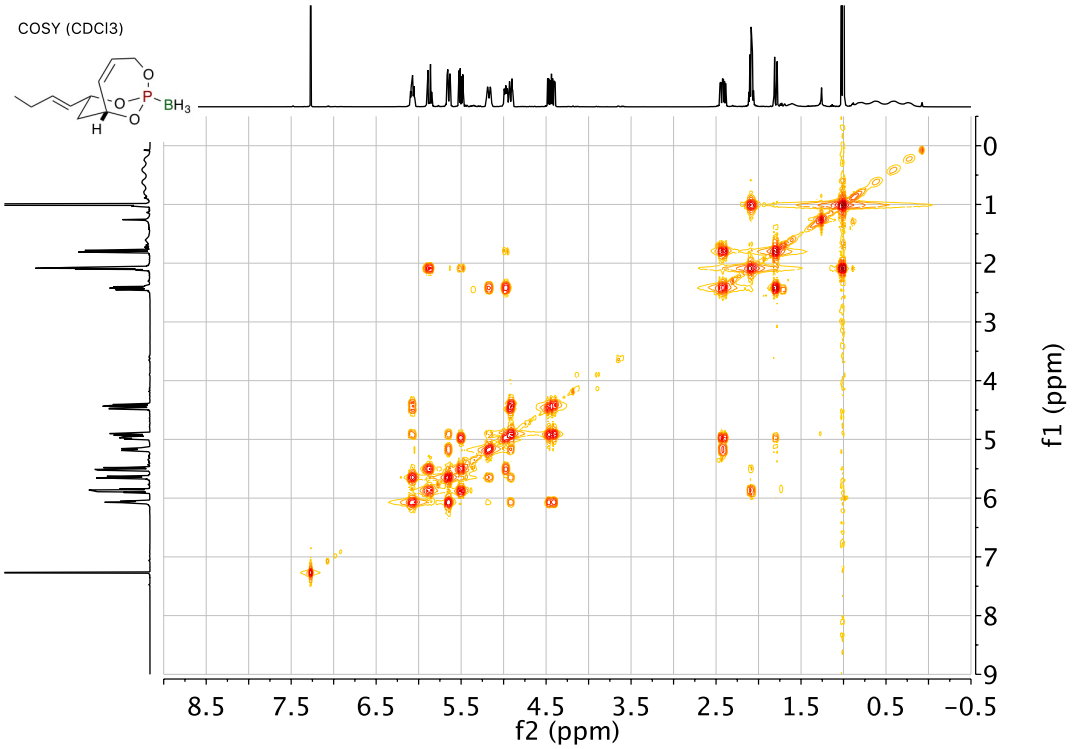


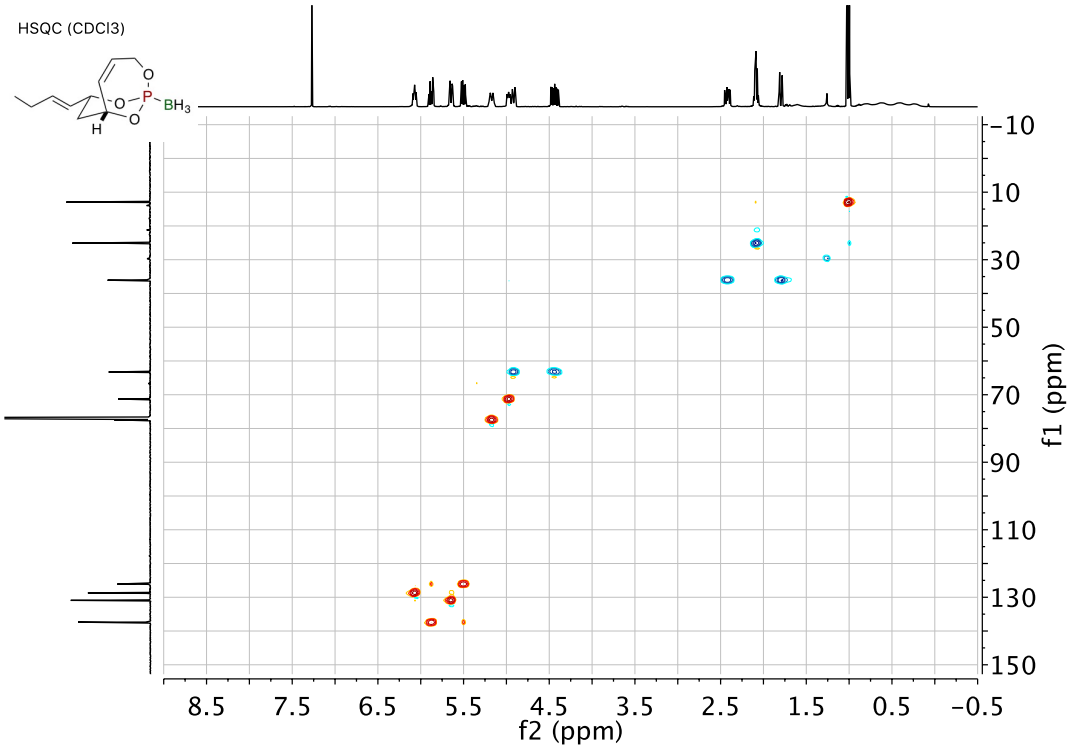

3.11.1

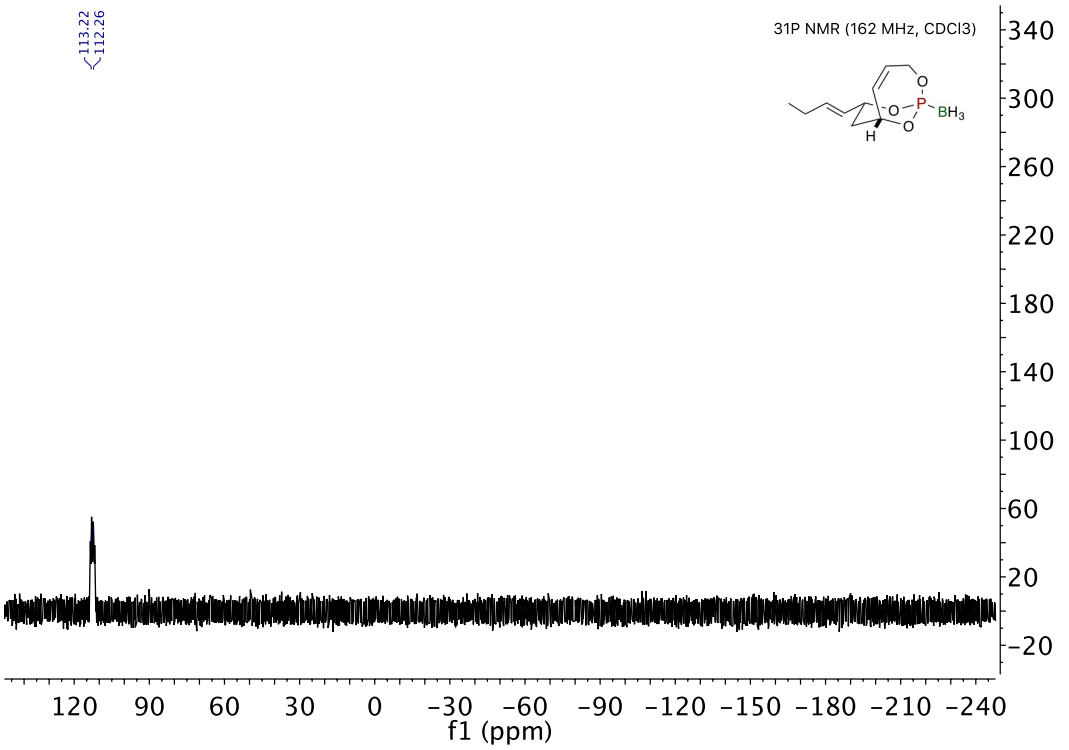


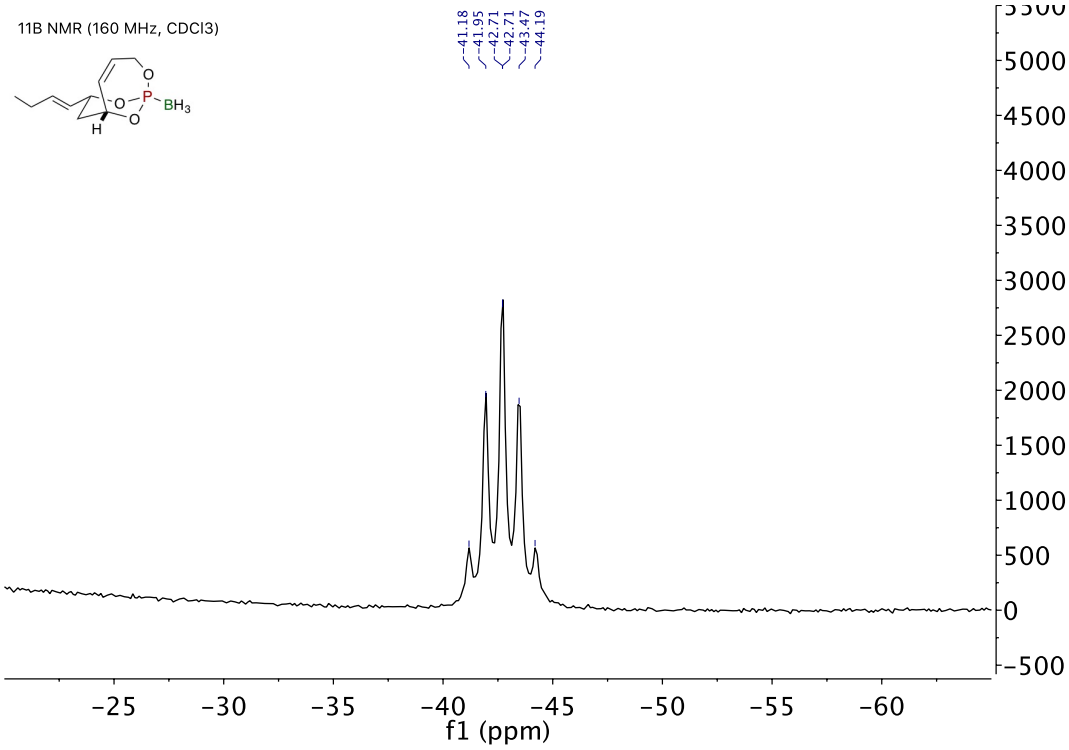

13C NMR (126 MHz, CDCl3)
137.37
130.92
128.71
126.08
126.02
77.49
77.42
77.25
77.00
76.75
71.32
71.26
63.33
63.27
36.07
36.02
25.10
12.92
220000
200000
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
-20000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)


13C NMR {1H} (126 MHz, CDCl3)
137.41
130.96
128.74
126.12
126.06
77.53
77.46
71.36
71.30
63.37
63.31
36.11
36.06
25.14
12.96
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
-10000
-15000
-20000
210
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

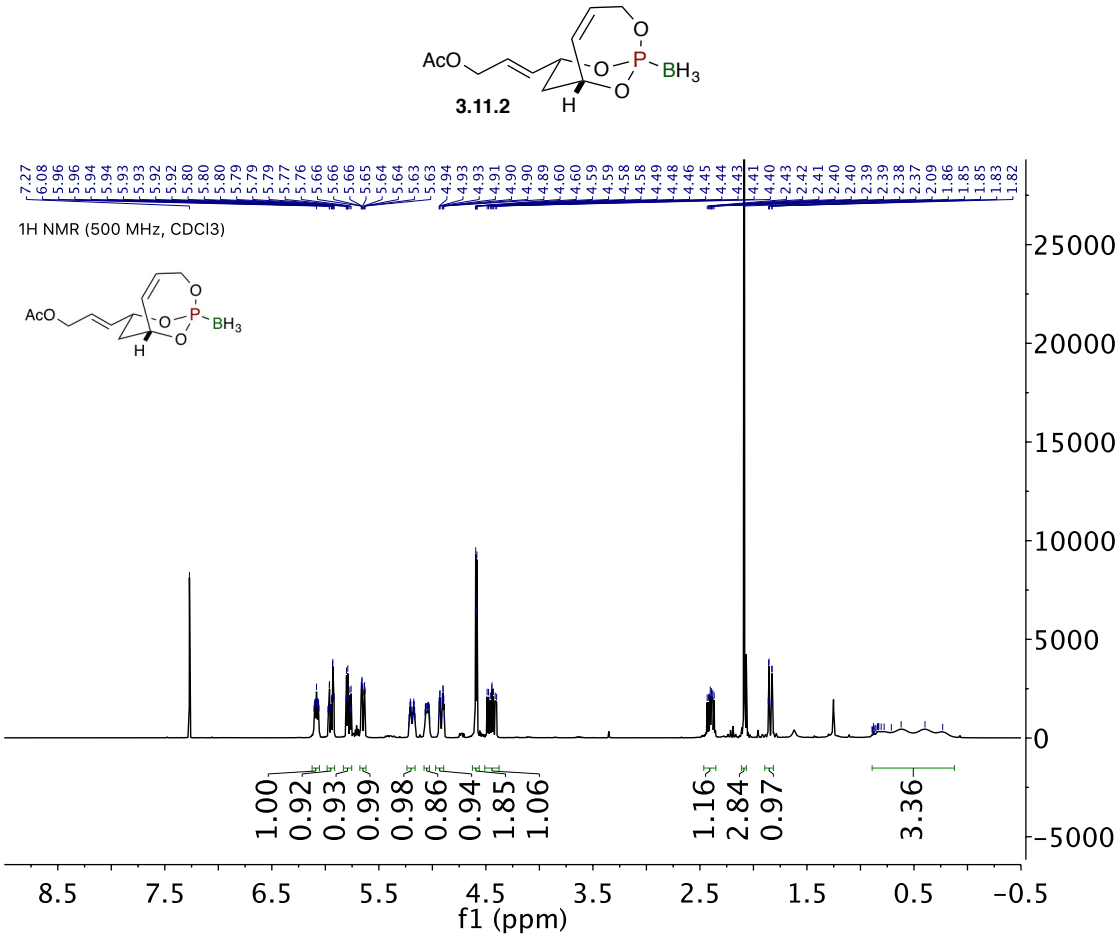

COSY (CDCl3)
BH3
f2 (ppm)
f1 (ppm)

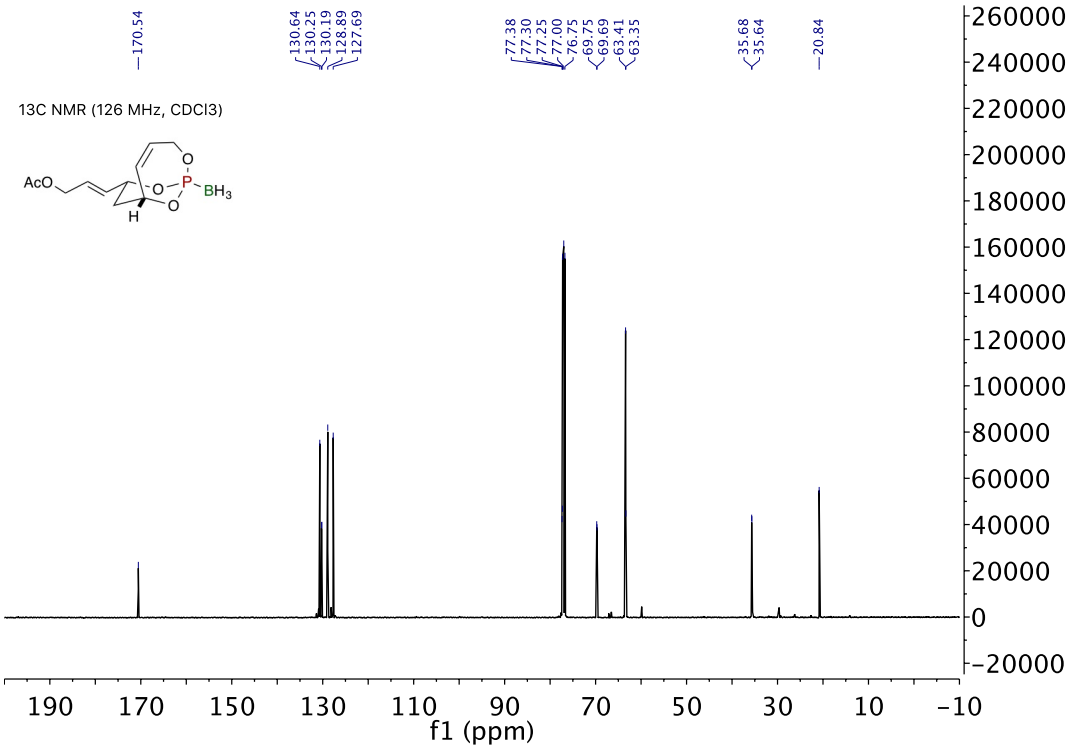

HSQC (CDCl3)
BH3
f2 (ppm)
f1 (ppm)

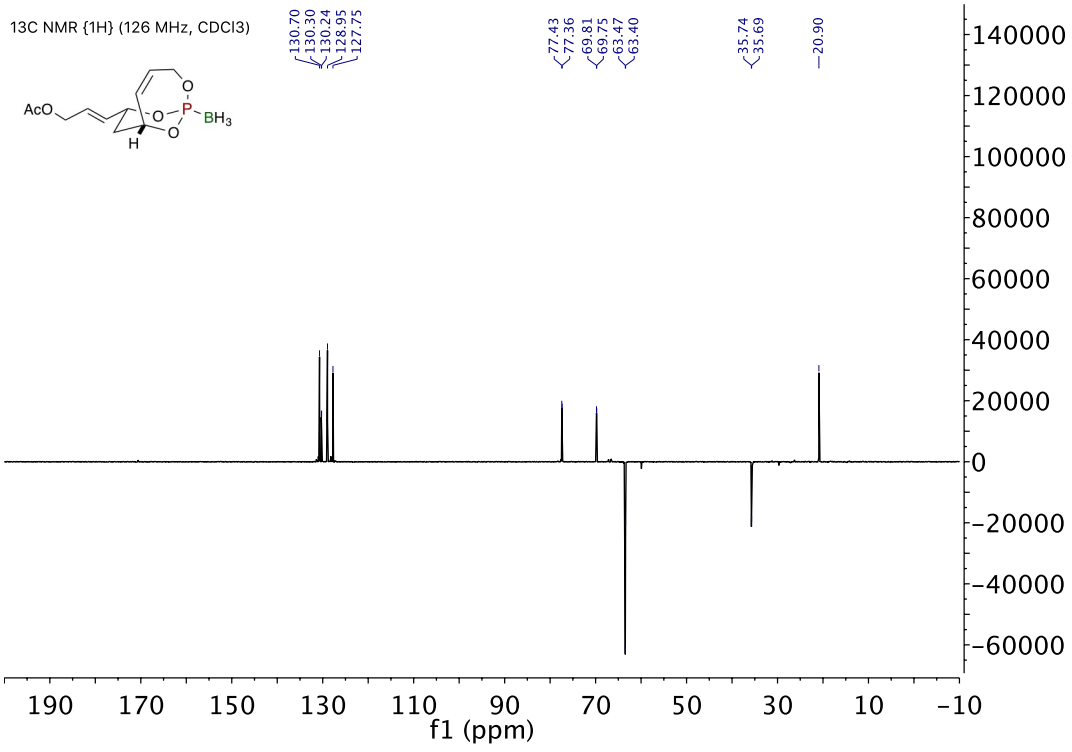

31P NMR (162 MHz, CDCl3)
113.22
112.26
340
300
260
220
180
140
100
60
20
-20
120 90 60 30 0 -30 -60 -90 -120 -150 -180 -210 -240
f1 (ppm)

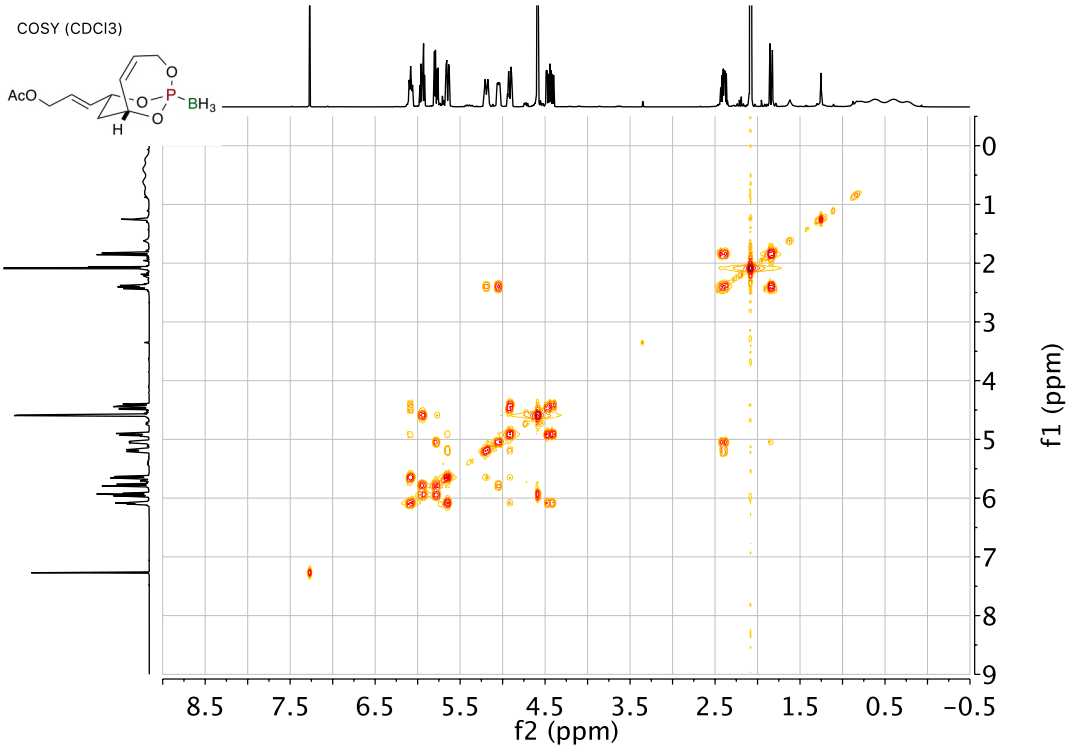

11B NMR (160 MHz, CDCl3)
-41.18
-41.95
-42.71
-42.71
-43.47
-44.19
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
-25 -30 -35 -40 -45 -50 -55 -60
f1 (ppm)

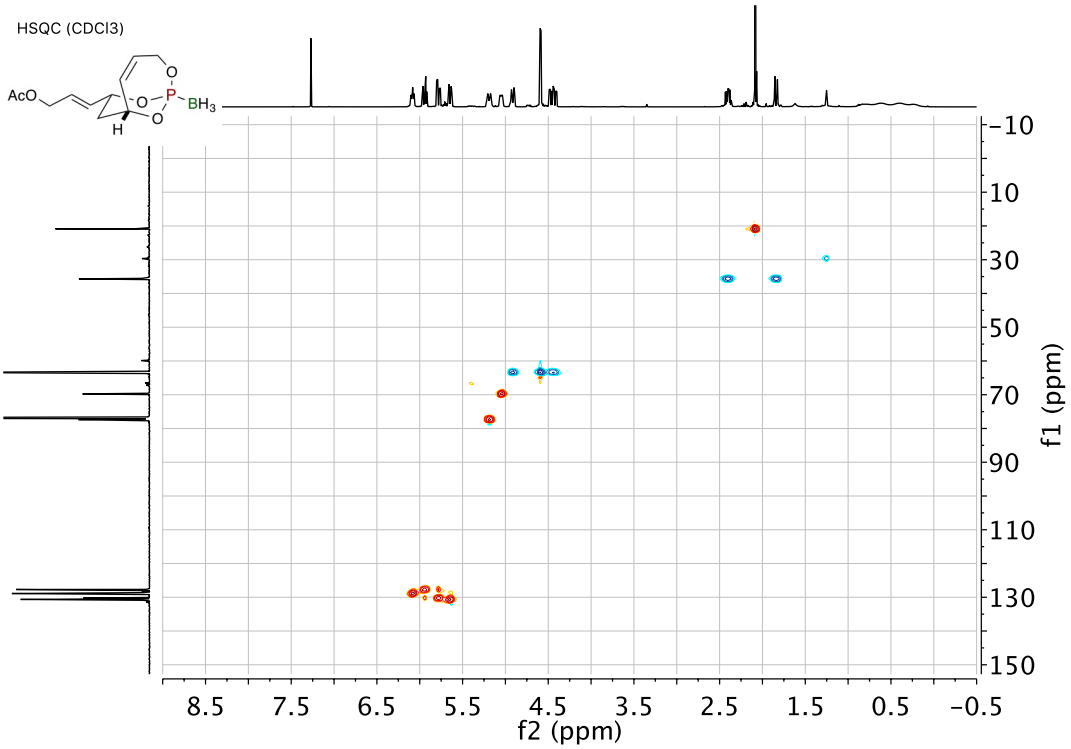
**(*E*)-3-((1*R*,6*R*,8*R*)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl)allyl acetate 1-borane ($C_{11}H_{18}BO_5P$, 3.11.2)**

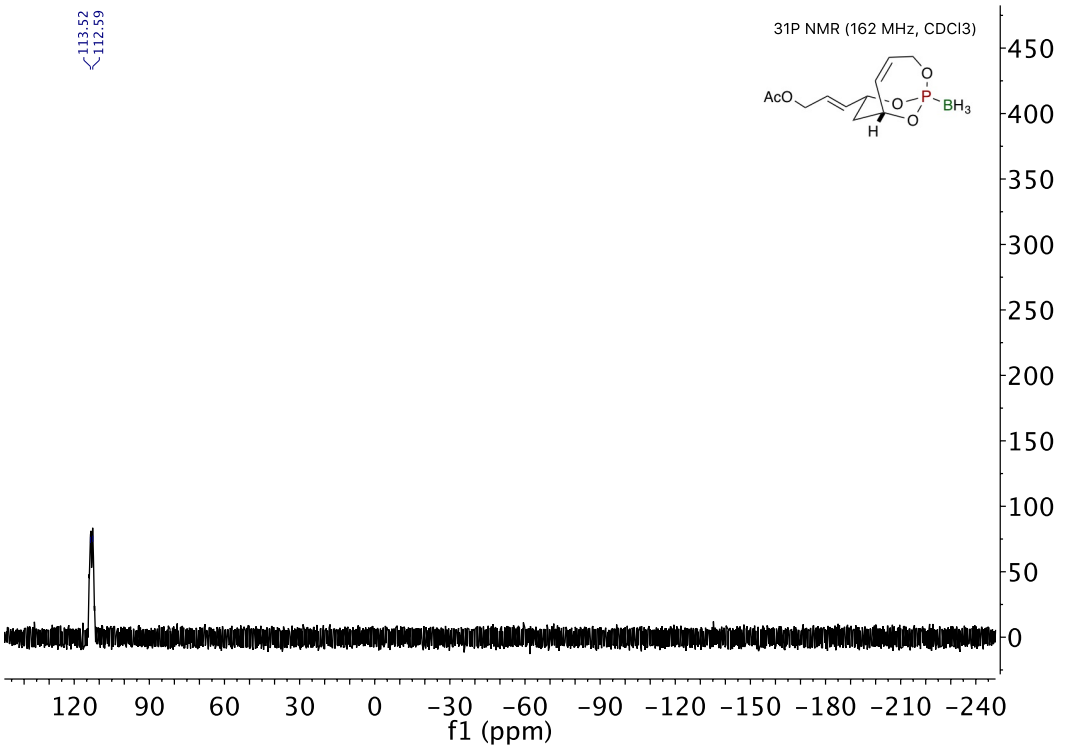


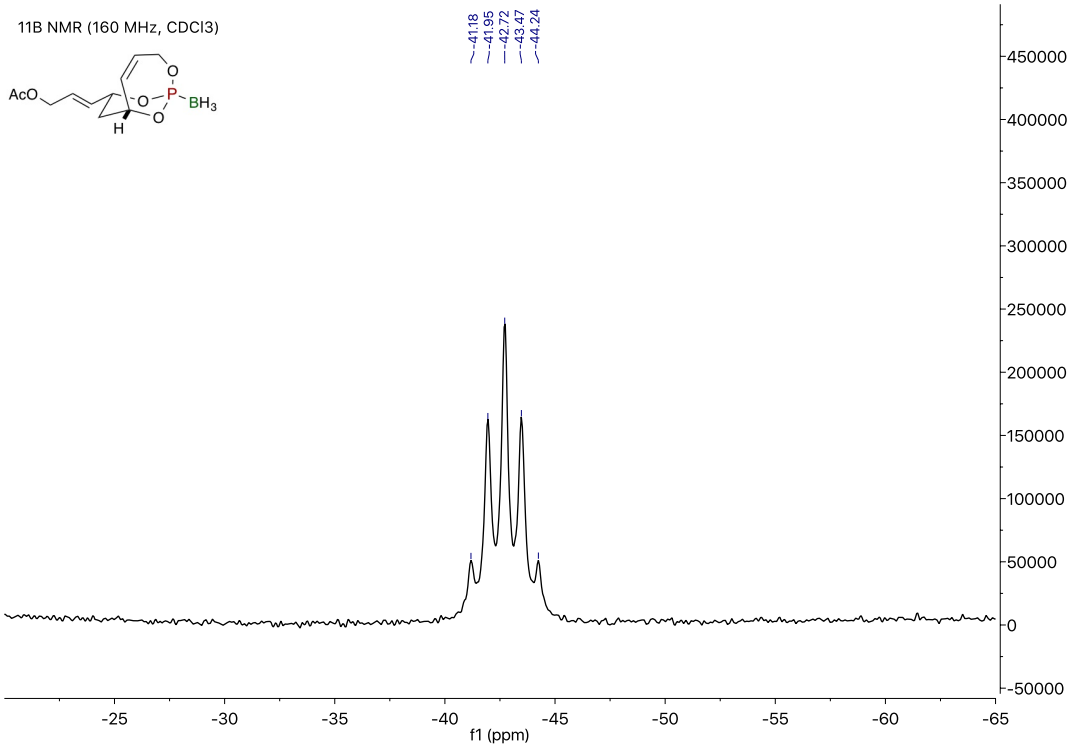

13C NMR (126 MHz, CDCl3)
170.54
130.64
130.25
130.19
128.89
127.69
77.38
77.30
77.25
77.00
76.75
69.75
69.69
63.41
63.35
35.68
35.64
20.84
AcO
O
O
P
BH3
O
H
260000
240000
220000
200000
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
-20000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)


13C NMR {1H} (126 MHz, CDCl3)
130.70
130.30
130.24
128.95
127.75
77.43
77.36
69.81
69.75
63.47
63.40
35.74
35.69
20.90
AcO
O
O
P
BH3
O
H
140000
120000
100000
80000
60000
40000
20000
0
-20000
-40000
-60000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)


COSY (CDCl3)
AcO
O
O
P
BH3
O
H
0
1
2
3
4
5
6
7
8
9
f1 (ppm)
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f2 (ppm)

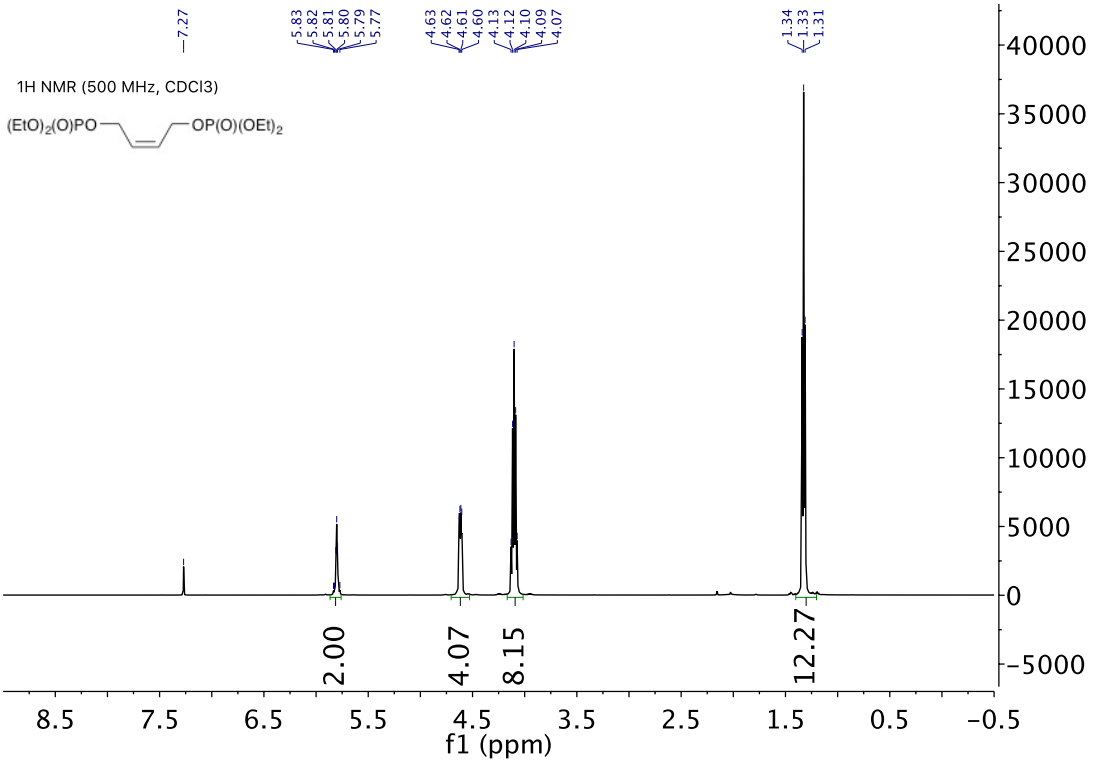

HSQC (CDCl3)
AcO
O
O
P
BH3
O
H
-10
10
30
50
70
90
110
130
150
f1 (ppm)
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f2 (ppm)

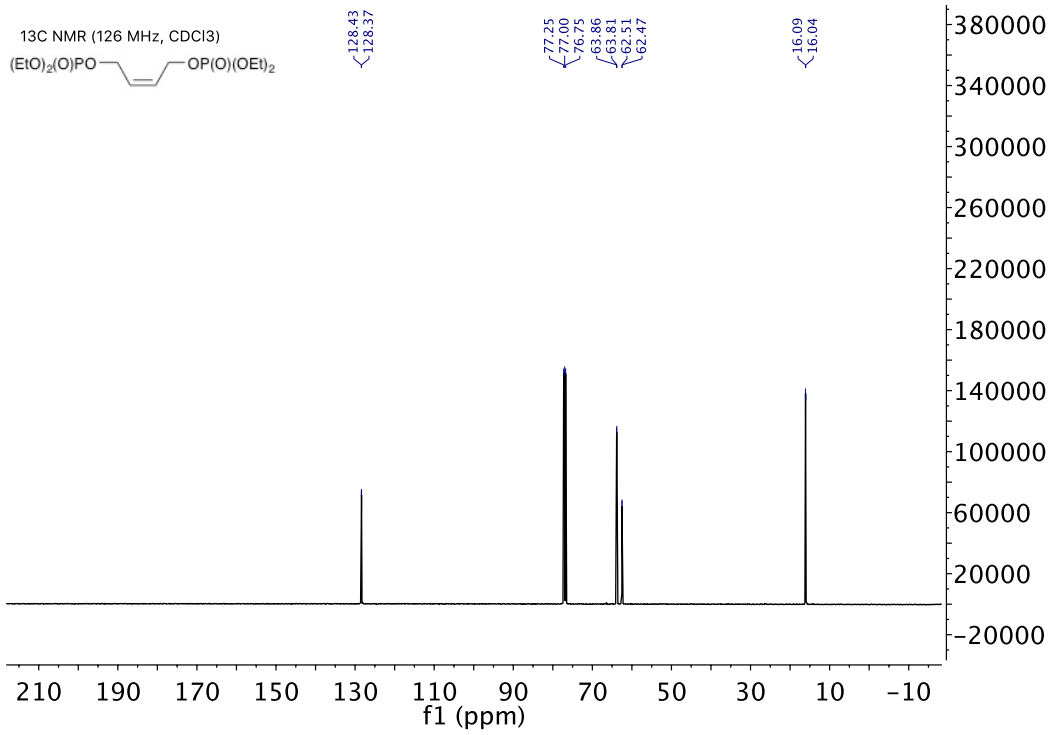

31P NMR (162 MHz, CDCl3)
113.52
112.59
AcO
O
O
P
BH3
O
H
450
400
350
300
250
200
150
100
50
0
120
90
60
30
0
-30
-60
-90
-120
-150
-180
-210
-240
f1 (ppm)

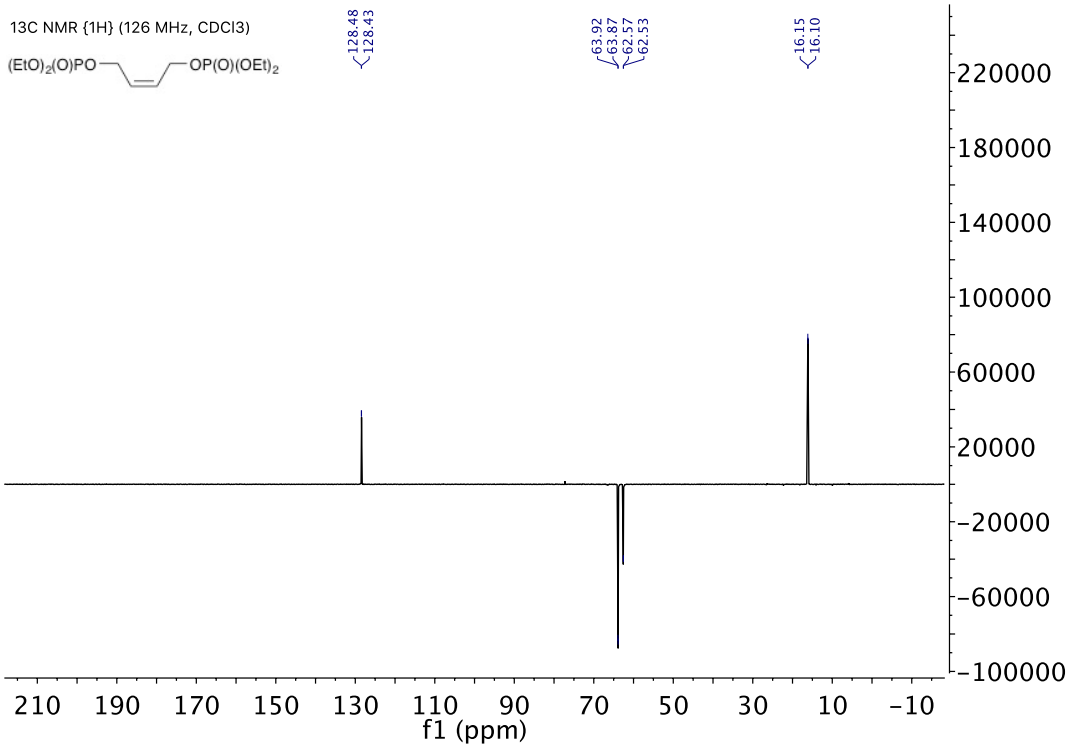

11B NMR (160 MHz, CDCl3)
-41.18
-41.95
-42.72
-43.47
-44.24
AcO
O
O
P
BH3
O
H
450000
400000
350000
300000
250000
200000
150000
100000
50000
0
-50000
-25
-30
-35
-40
-45
-50
-55
-60
-65
f1 (ppm)

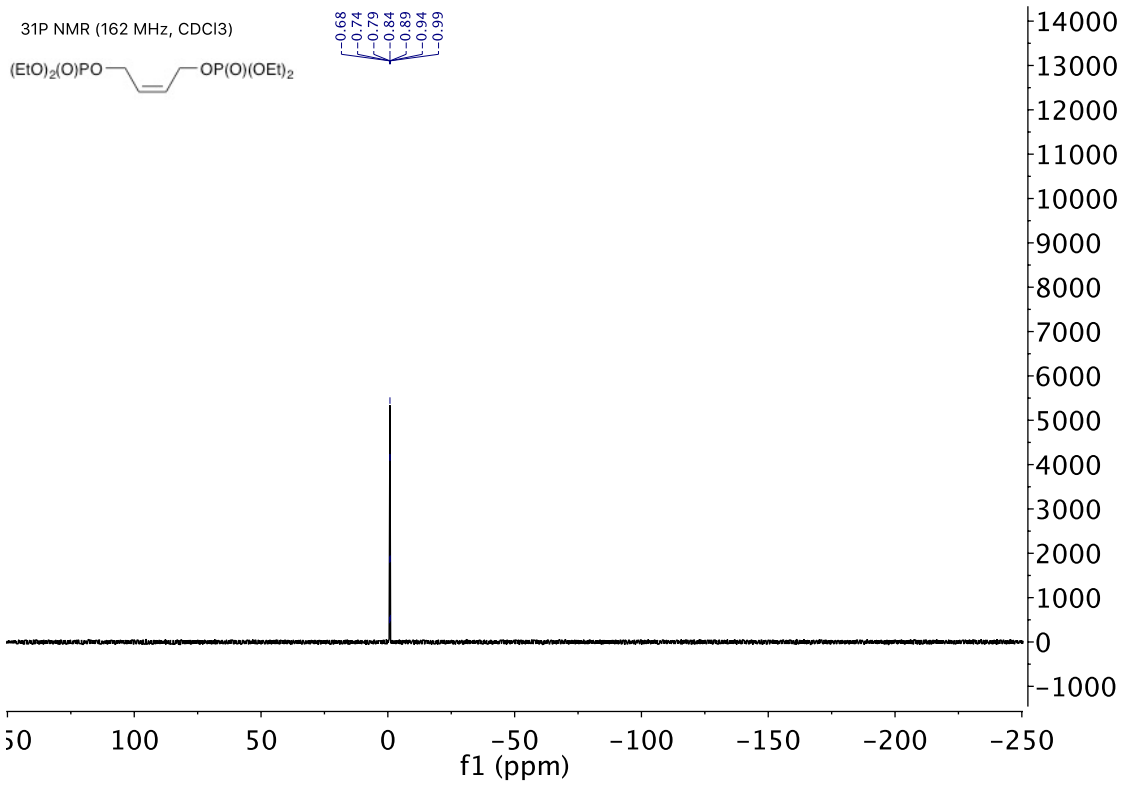
**(*Z*)-but-2-ene-1,4-diyl tetraethyl bis(phosphate) ($C_{12}H_{26}O_8P_2$, 3.11.7-SI)**


**3.11.7-SI**

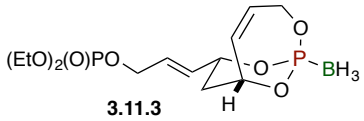



13C NMR (126 MHz, CDCl3)
(EtO)2(O)PO
OP(O)(OEt)2
128.43
128.37
77.25
77.00
76.75
63.86
63.81
62.51
62.47
16.09
16.04
380000
340000
300000
260000
220000
180000
140000
100000
60000
20000
-20000
210
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

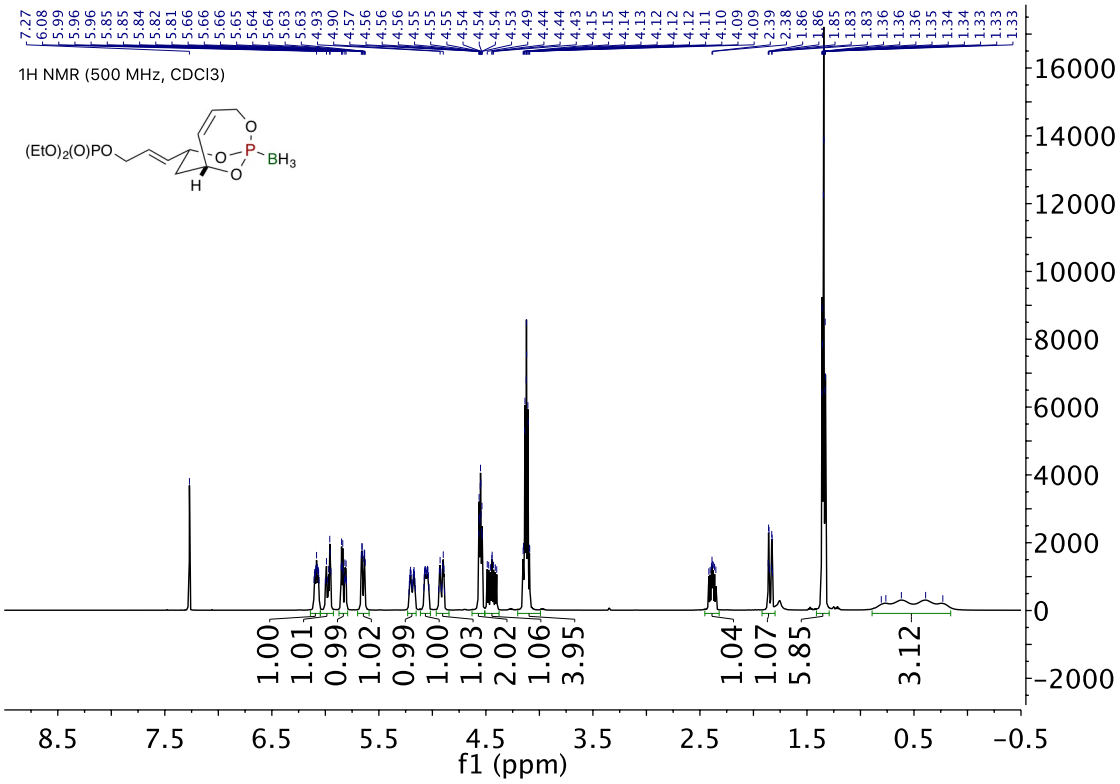

13C NMR {1H} (126 MHz, CDCl3)
(EtO)2(O)PO
OP(O)(OEt)2
128.48
128.43
63.92
63.87
62.57
62.53
16.15
16.10
220000
180000
140000
100000
60000
20000
-20000
-60000
-100000
210
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

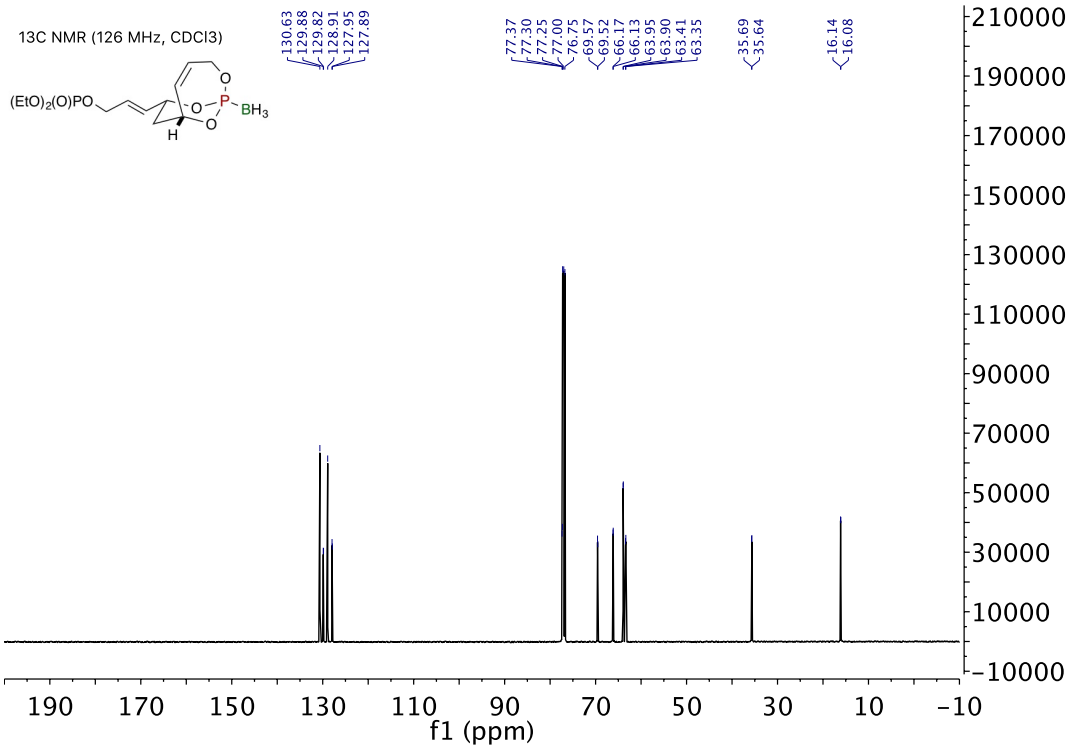

31P NMR (162 MHz, CDCl3)
(EtO)2(O)PO
OP(O)(OEt)2
0.68
0.74
0.79
0.84
0.89
0.94
0.99
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
50
100
50
0
-50
-100
-150
-200
-250
f1 (ppm)

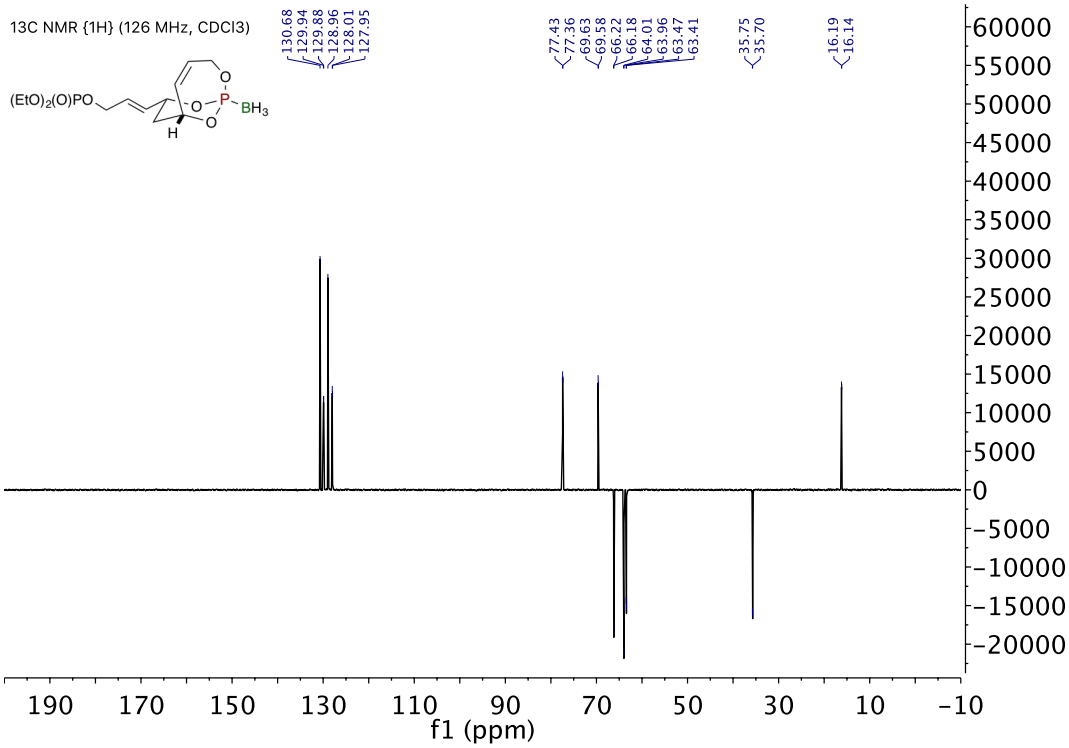
**(*E*)-3-((1*S*,6*R*,8*R*)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl-1-borane)allyl diethyl phosphate ($C_{13}H_{25}BO_7P_2$, 3.11.3)**

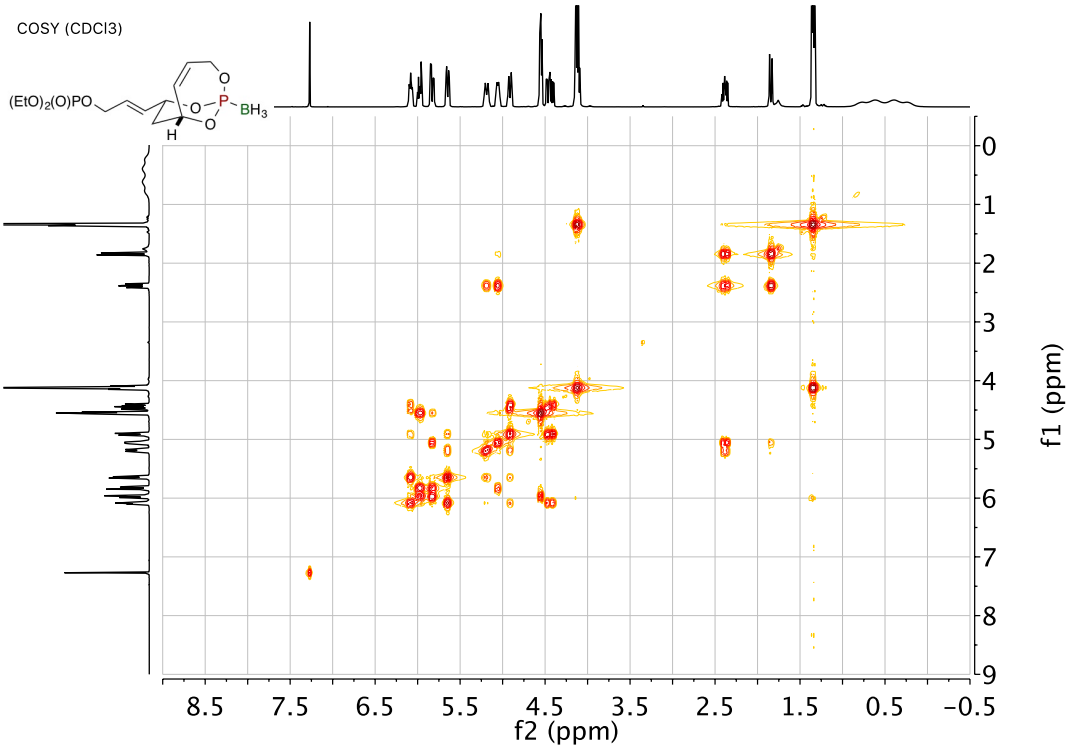


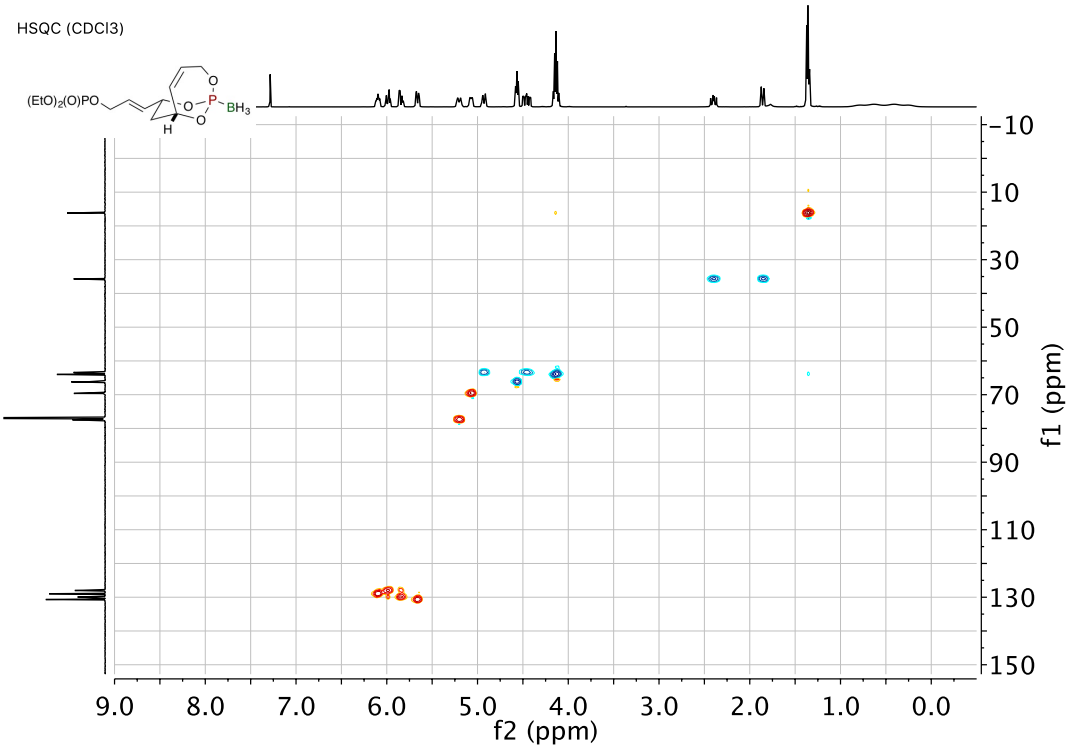

3.11.3

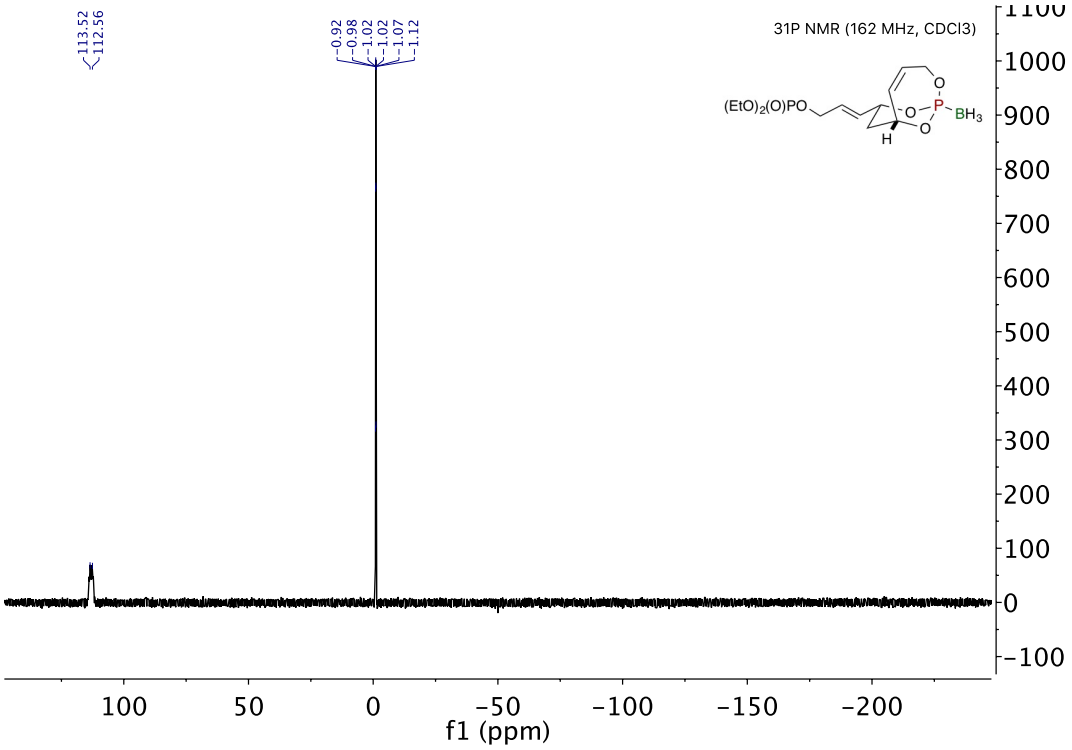


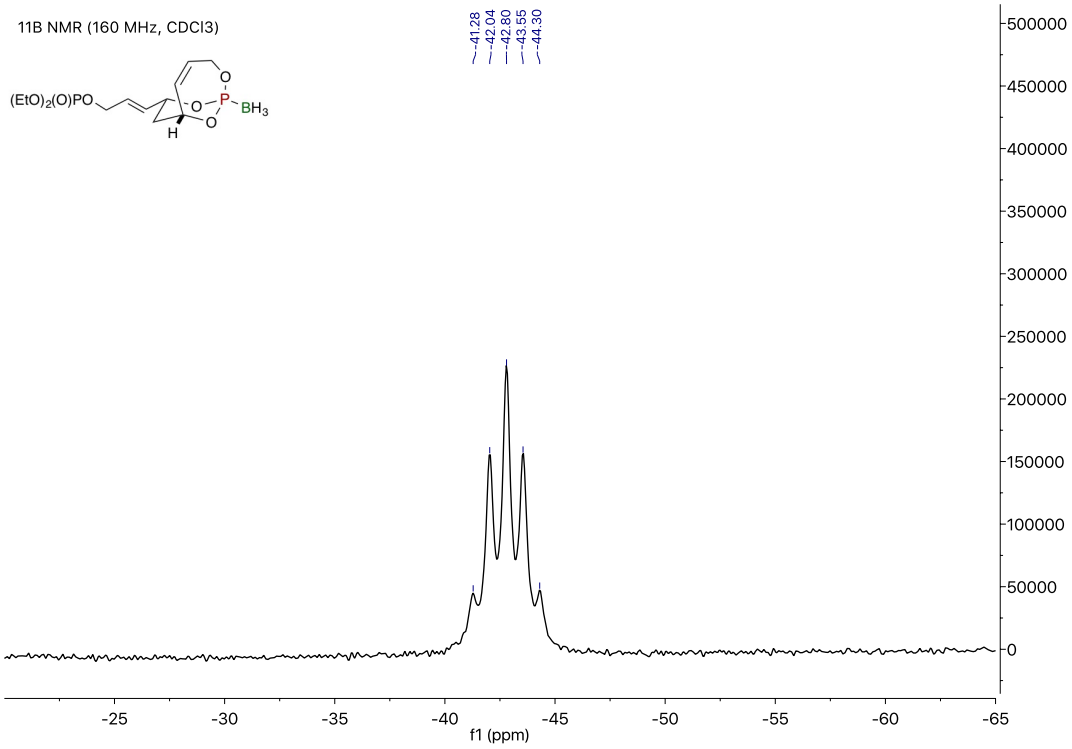

13C NMR (126 MHz, CDCl3)
(EtO)2(O)PO
BH3
H
130.63
129.88
129.82
128.91
127.95
127.89
77.37
77.30
77.25
77.00
76.75
69.57
69.52
66.17
66.13
63.95
63.90
63.41
63.35
35.69
35.64
16.14
16.08
210000
190000
170000
150000
130000
110000
90000
70000
50000
30000
10000
-10000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)


13C NMR {1H} (126 MHz, CDCl3)
(EtO)2(O)PO
BH3
H
130.68
129.94
129.88
128.96
128.01
127.95
77.43
77.36
69.63
69.58
66.22
66.18
64.01
63.96
63.47
63.41
35.75
35.70
16.19
16.14
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
-10000
-15000
-20000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

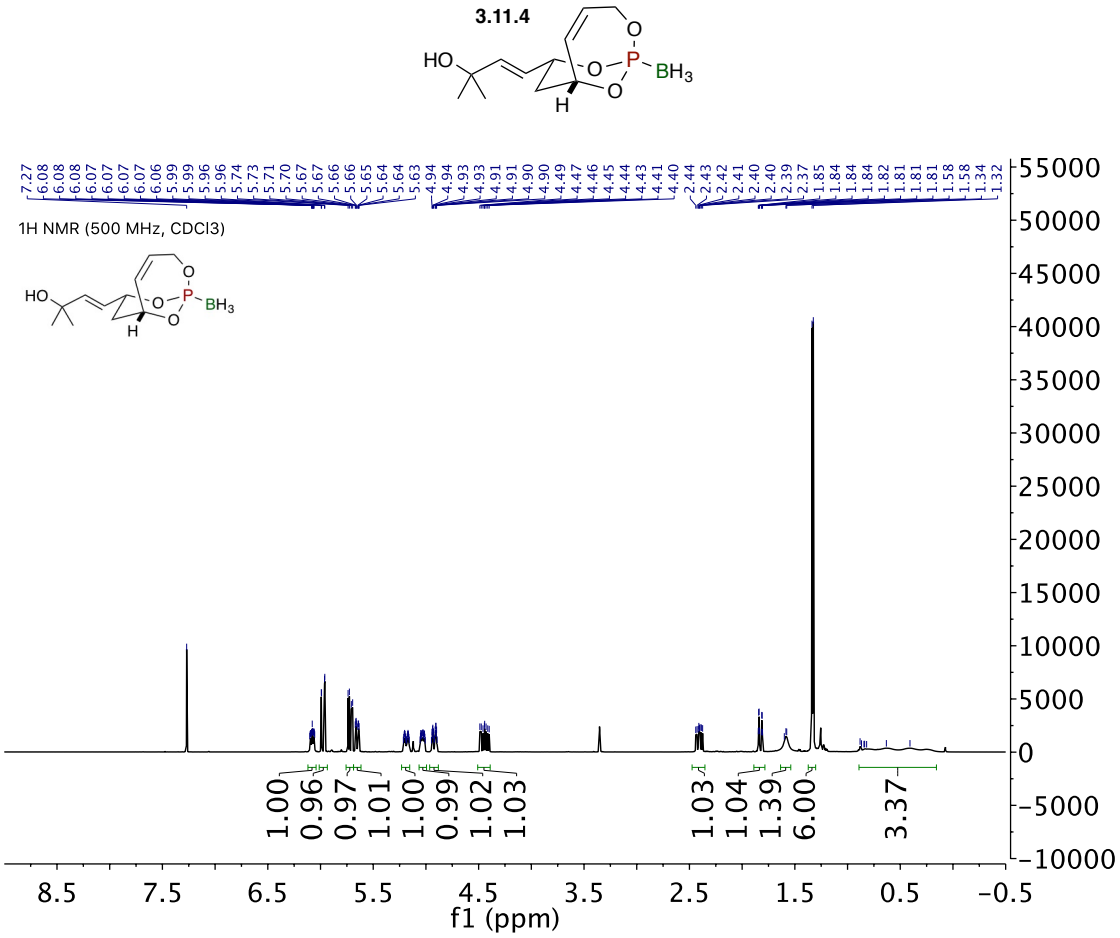

COSY (CDCl3)
(EtO)2(O)PO
BH3
H
f2 (ppm)
f1 (ppm)

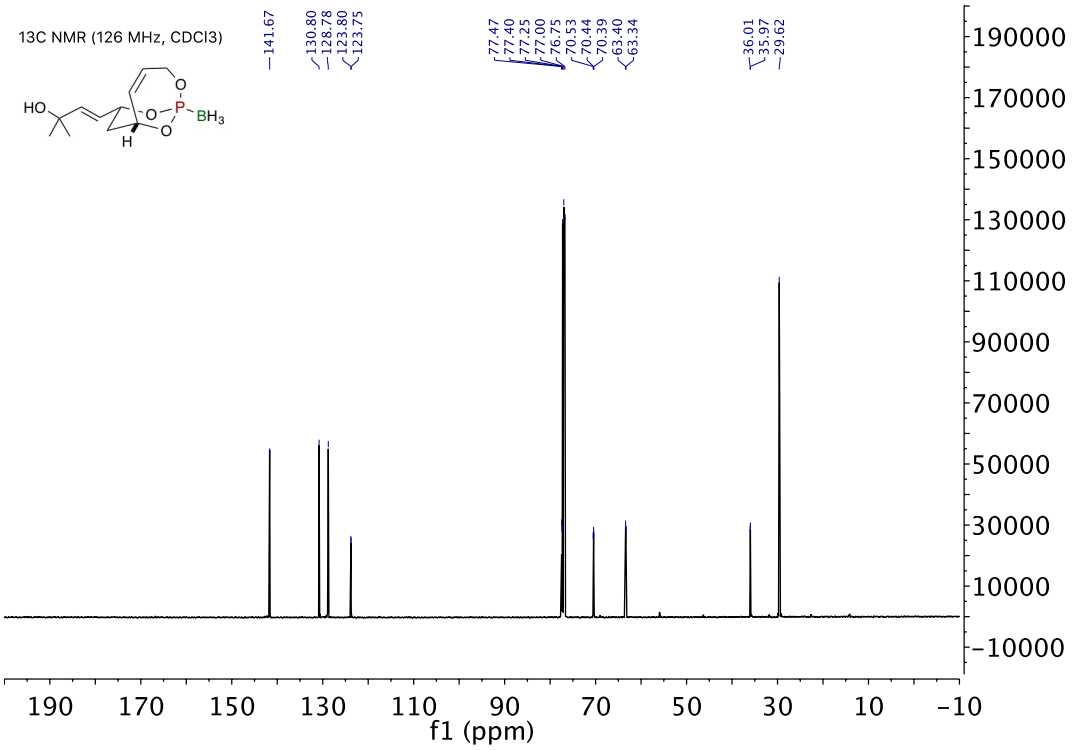

HSQC (CDCl3)
(EtO)2(O)PO
BH3
H
f2 (ppm)
f1 (ppm)

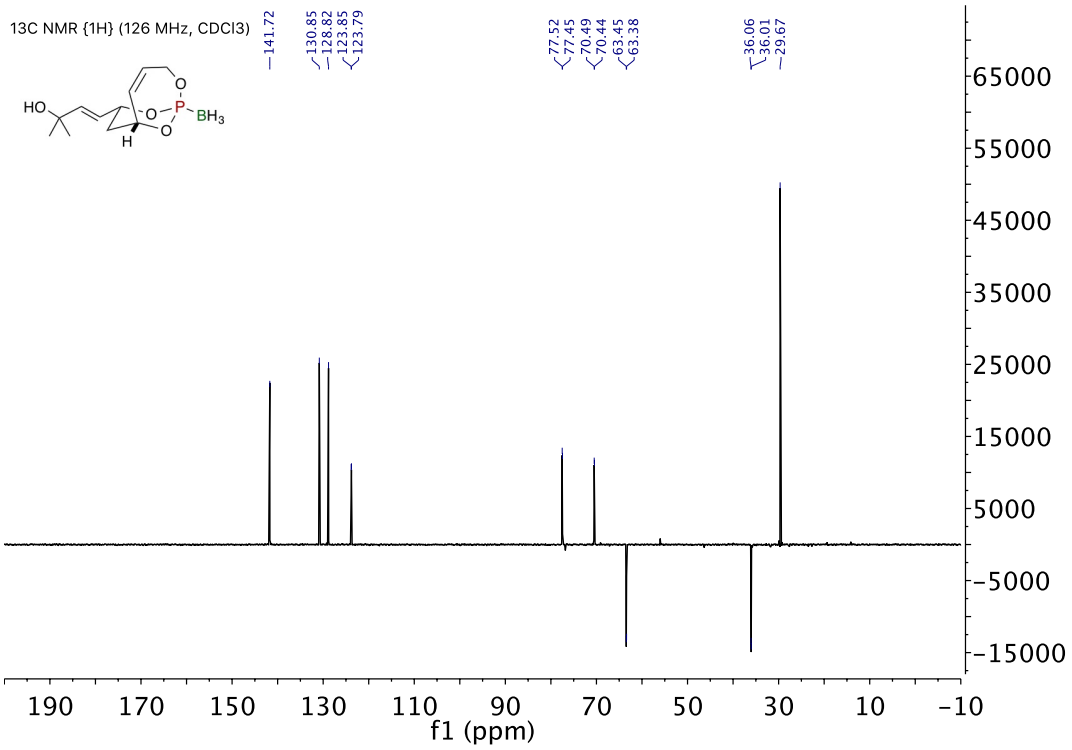

31P NMR (162 MHz, CDCl3)
(EtO)2(O)PO
BH3
H
113.52
112.56
0.92
0.98
1.02
1.02
1.07
1.12
f1 (ppm)

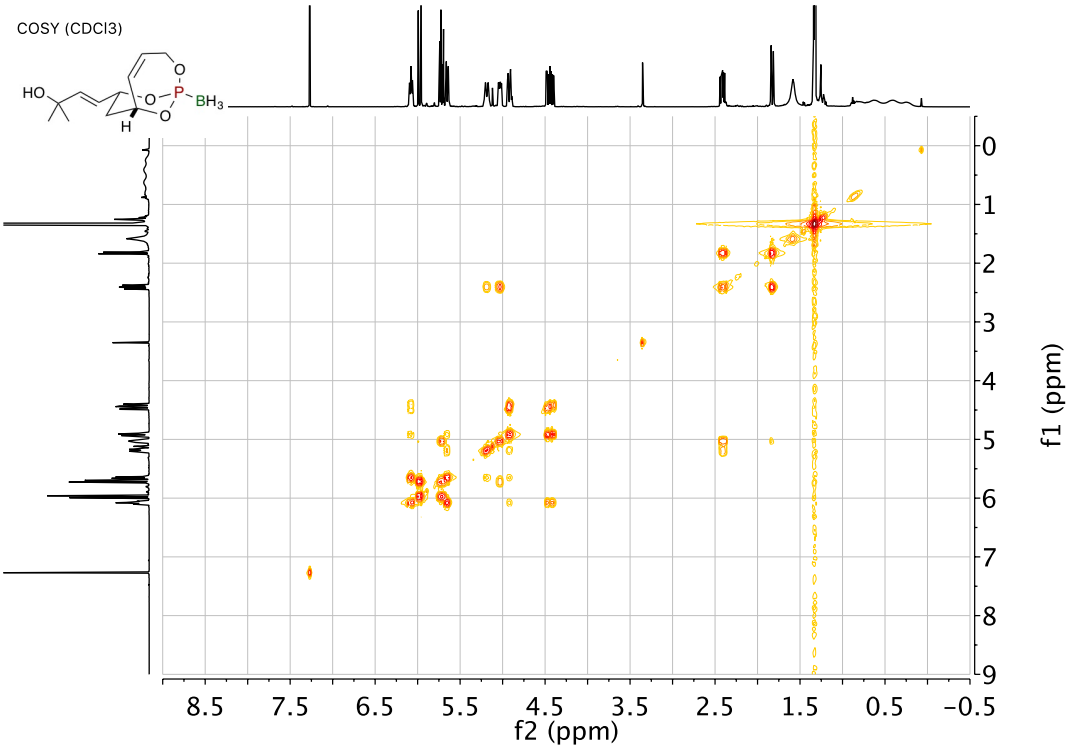

11B NMR (160 MHz, CDCl3)
(EtO)2(O)PO
BH3
H
41.28
42.04
42.80
43.55
44.30
f1 (ppm)

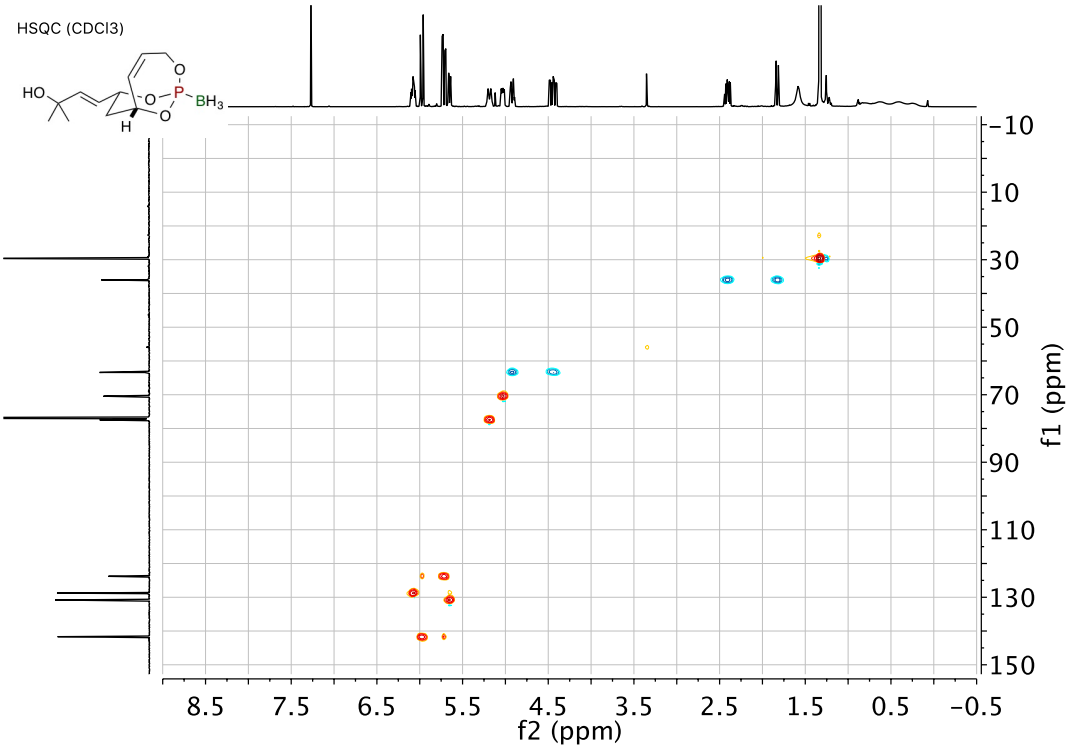
**(*E*)-4-((1*S*,6*R*,8*R*)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl-1-borane)-2-methylbut-3-en-2-ol ($C_{11}H_{20}BO_4P$, 3.11.4)**

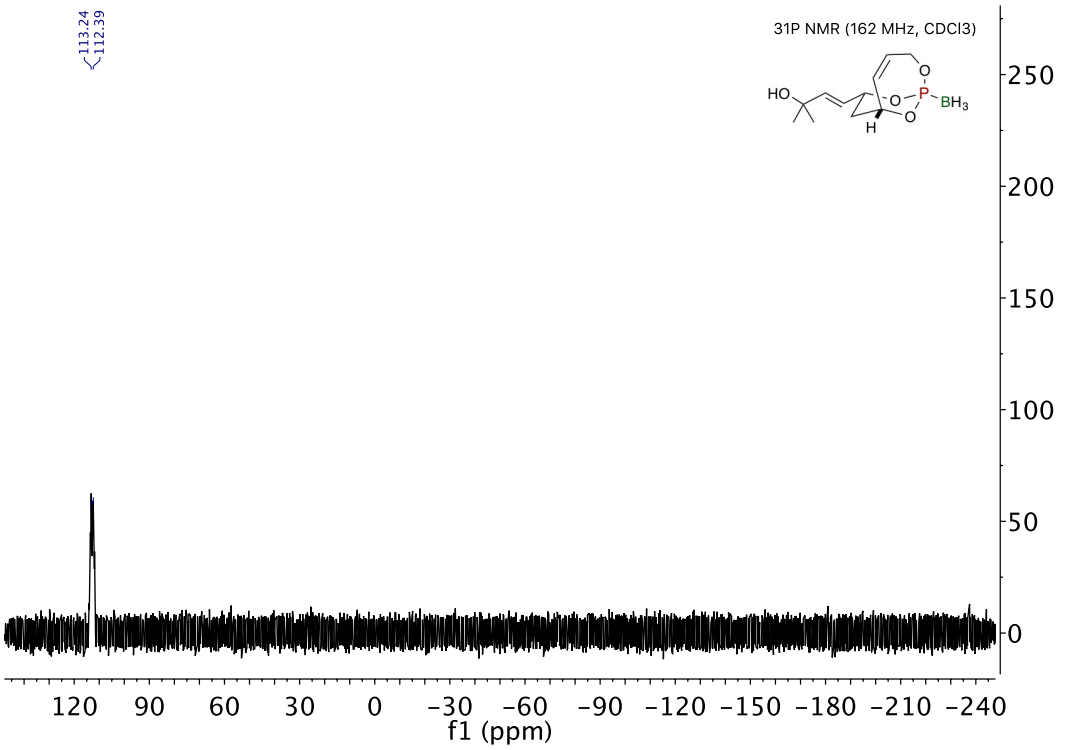


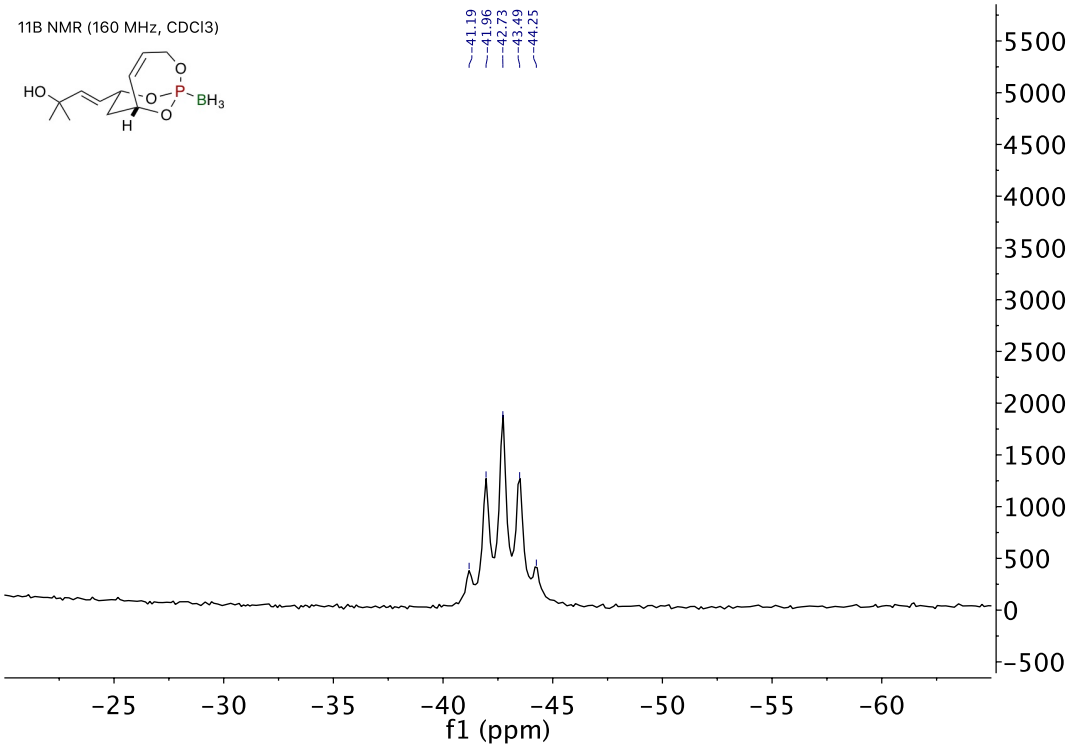

13C NMR (126 MHz, CDCl3)
141.67
130.80
128.78
123.80
123.75
77.47
77.40
77.25
77.00
76.75
70.53
70.44
70.39
63.40
63.34
36.01
35.97
29.62
HO
O
P
BH3
O
O
H
190000
170000
150000
130000
110000
90000
70000
50000
30000
10000
-10000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)


13C NMR {1H} (126 MHz, CDCl3)
141.72
130.85
128.82
123.85
123.79
77.52
77.45
70.49
70.44
63.45
63.38
36.06
36.01
29.67
HO
O
P
BH3
O
O
H
65000
55000
45000
35000
25000
15000
5000
-5000
-15000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

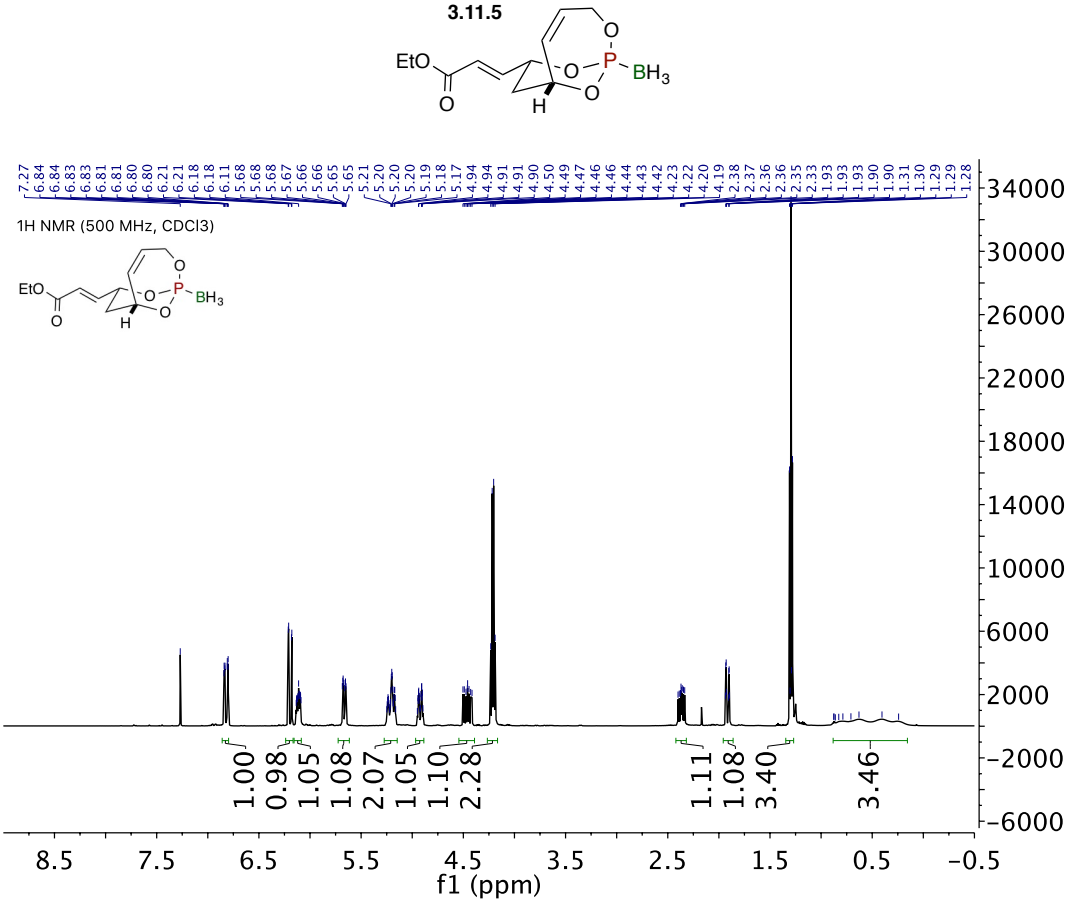

COSY (CDCl3)
HO
O
P
BH3
O
O
H
0
1
2
3
4
5
6
7
8
9
f1 (ppm)
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f2 (ppm)

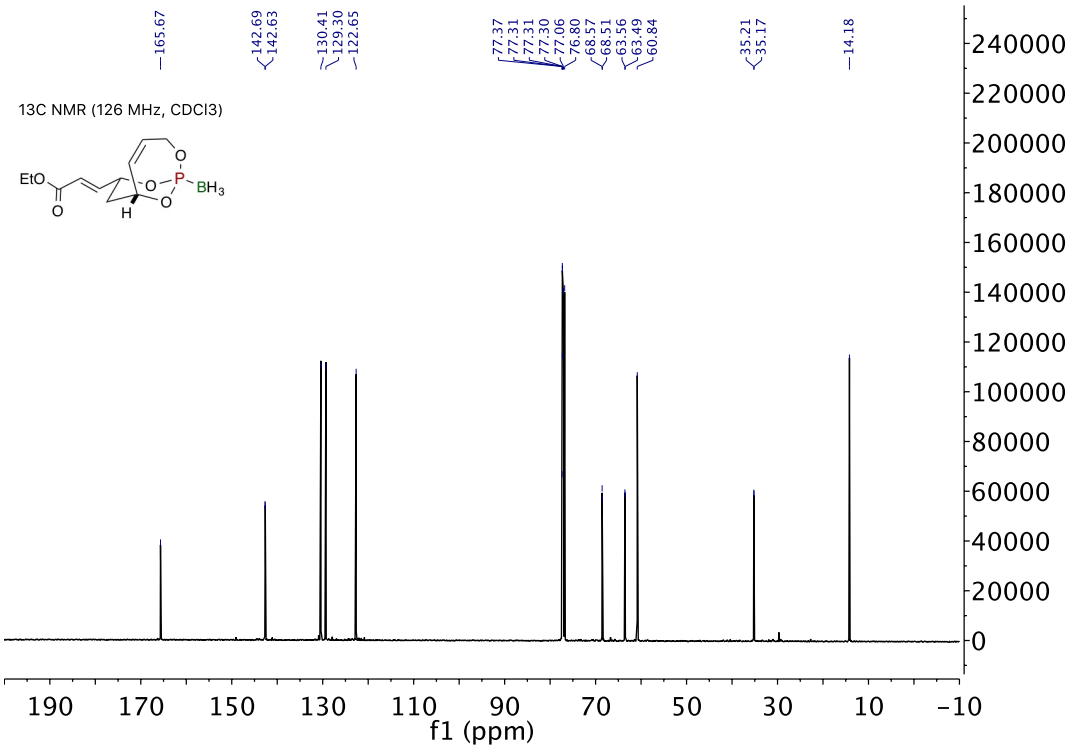

HSQC (CDCl3)
HO
O
P
BH3
O
O
H
-10
10
30
50
70
90
110
130
150
f1 (ppm)
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f2 (ppm)

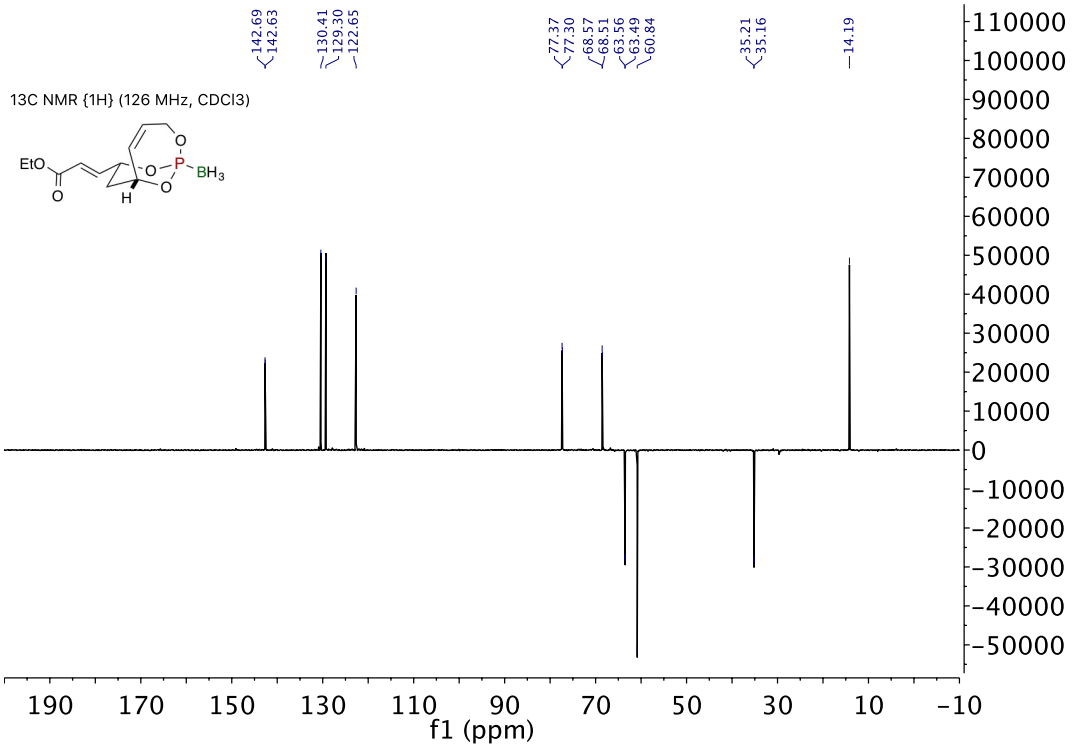

31P NMR (162 MHz, CDCl3)
113.24
112.39
HO
O
O
P
BH3
O
H
250
200
150
100
50
0
120 90 60 30 0 -30 -60 -90 -120 -150 -180 -210 -240
f1 (ppm)

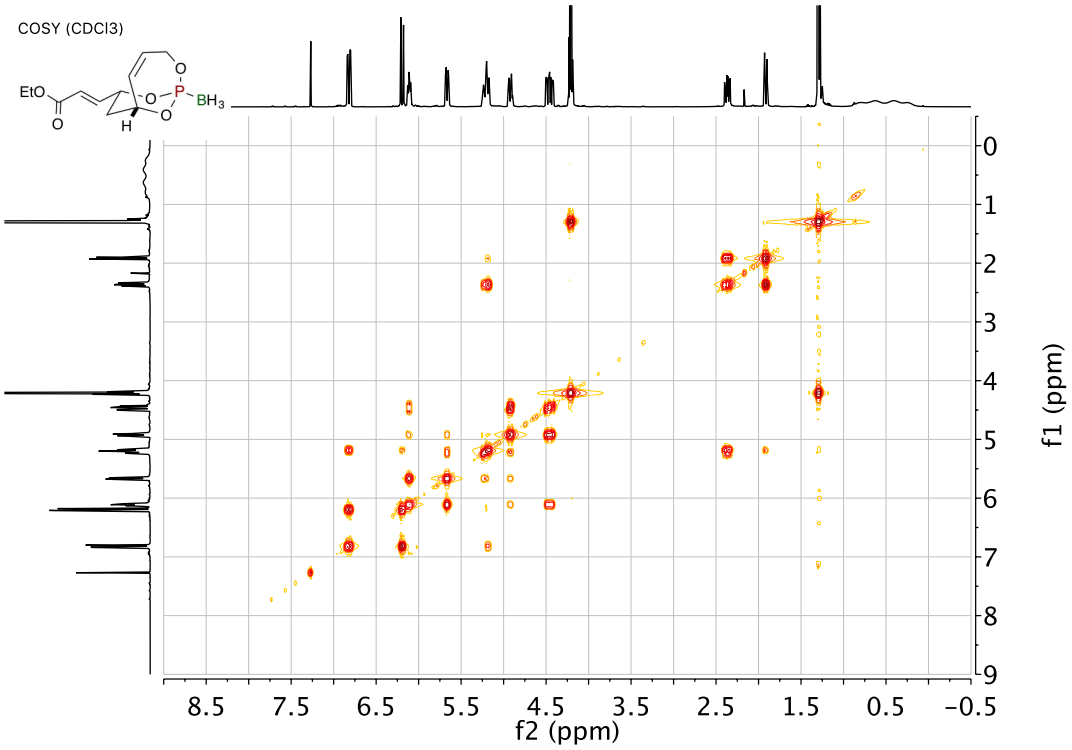

11B NMR (160 MHz, CDCl3)
-41.19
-41.96
-42.73
-43.49
-44.25
HO
O
O
P
BH3
O
H
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
-25 -30 -35 -40 -45 -50 -55 -60
f1 (ppm)

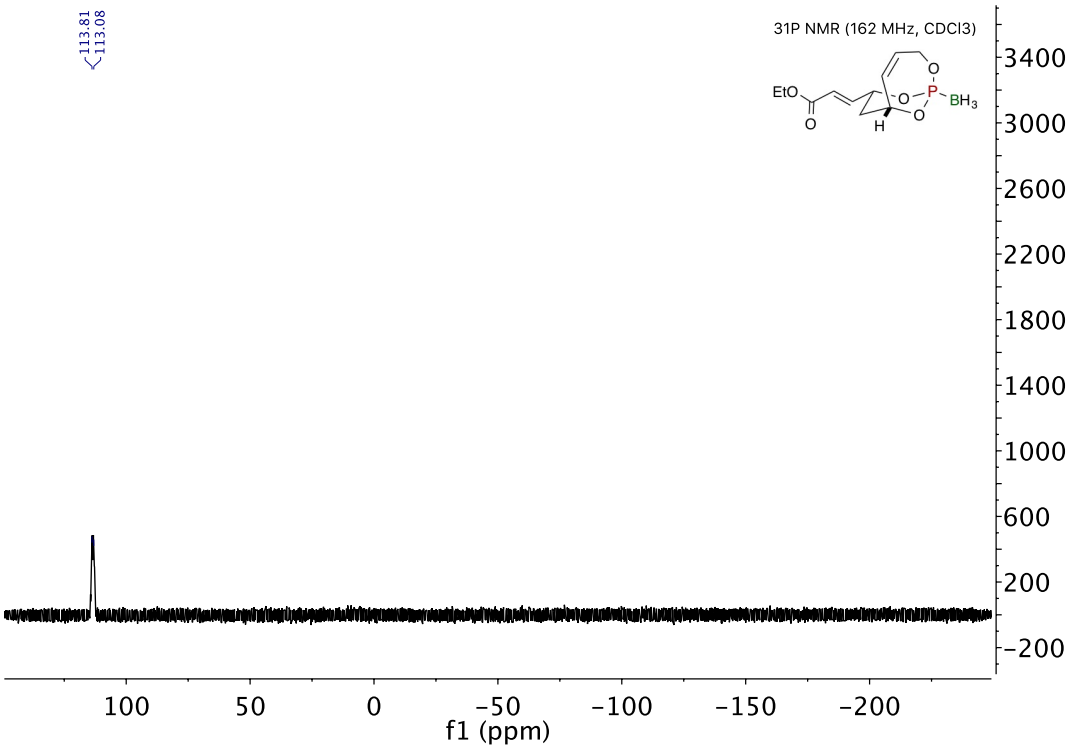
**(*E*)-ethyl 3-((1*S*,6*R*,8*R*)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl-1-borane)acrylate ($C_{11}H_{18}BO_5P$, 3.11.5)**

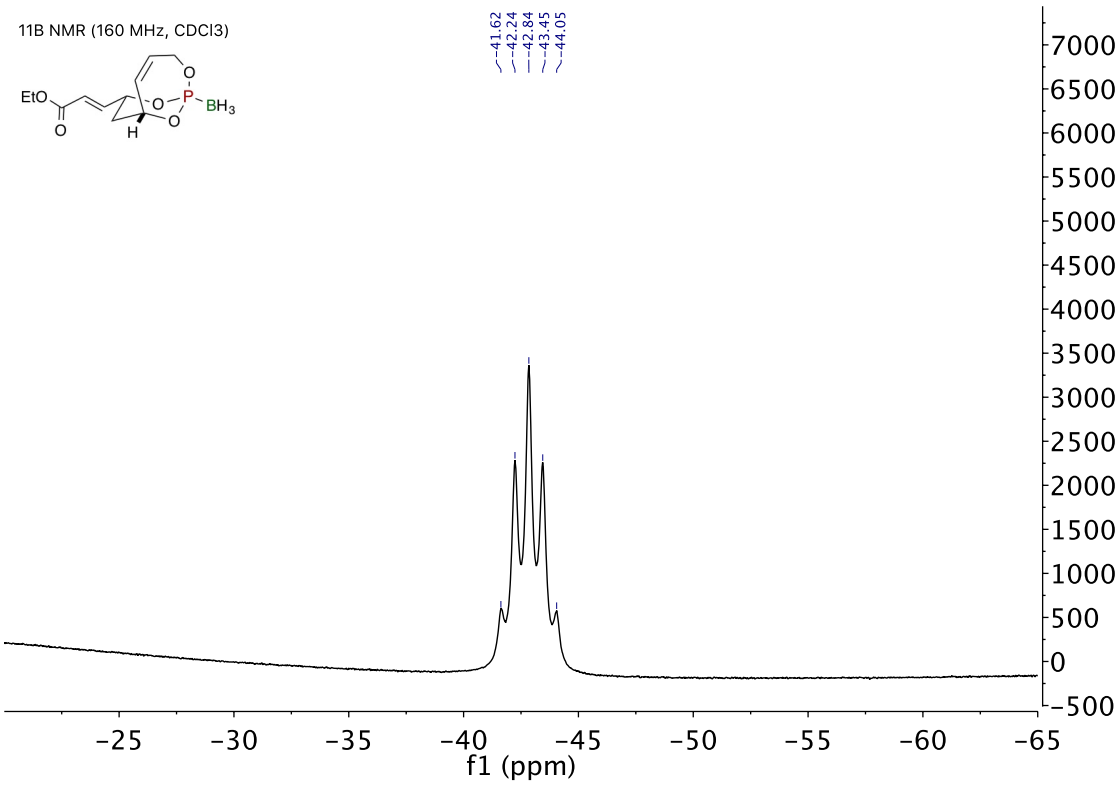



13C NMR (126 MHz, CDCl3)
165.67
142.69
142.63
130.41
129.30
122.65
77.37
77.31
77.31
77.30
77.06
76.80
68.57
68.51
63.56
63.49
60.84
35.21
35.17
14.18
EtO
O
O
O
O
P
BH3
H
240000
220000
200000
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

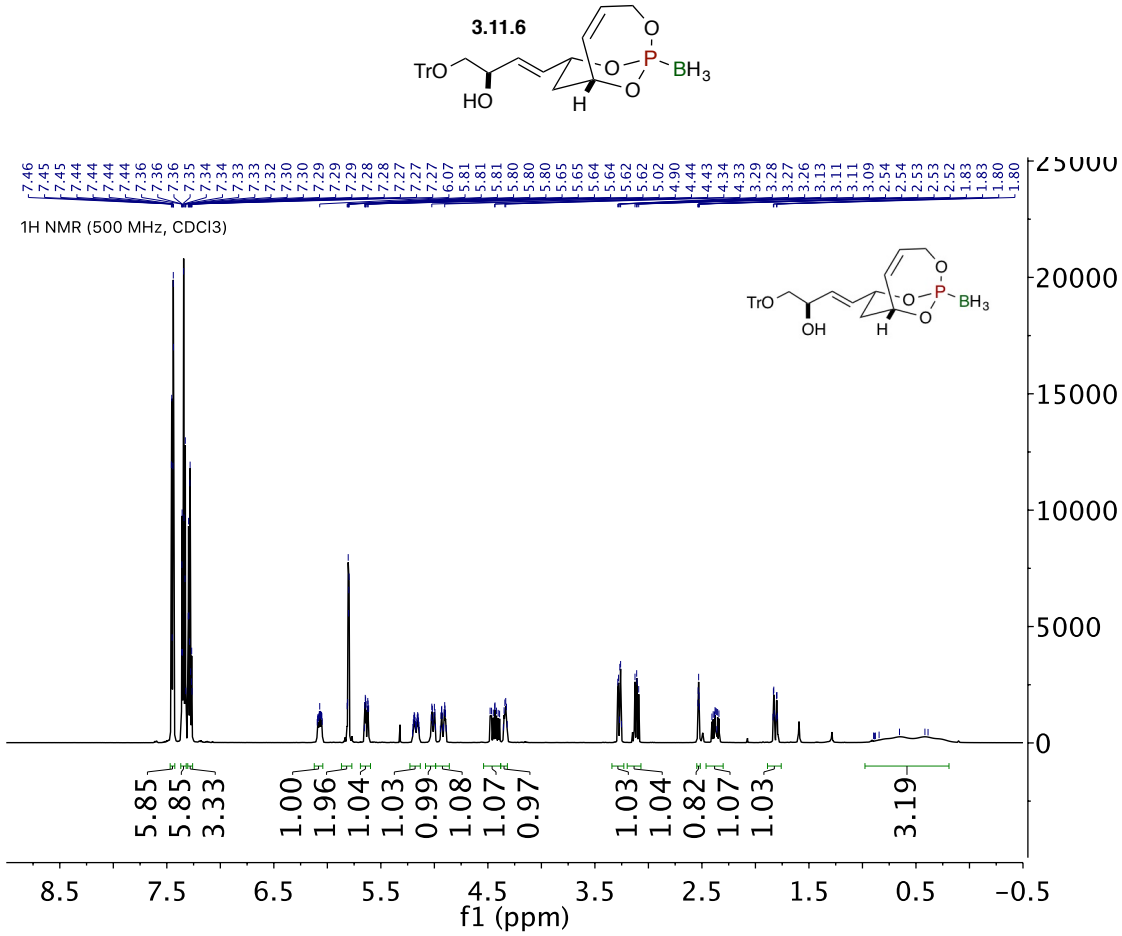

13C NMR {1H} (126 MHz, CDCl3)
142.69
142.63
130.41
129.30
122.65
77.37
77.30
68.57
68.51
63.56
63.49
60.84
35.21
35.16
14.19
EtO
O
O
O
O
P
BH3
H
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
-20000
-30000
-40000
-50000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

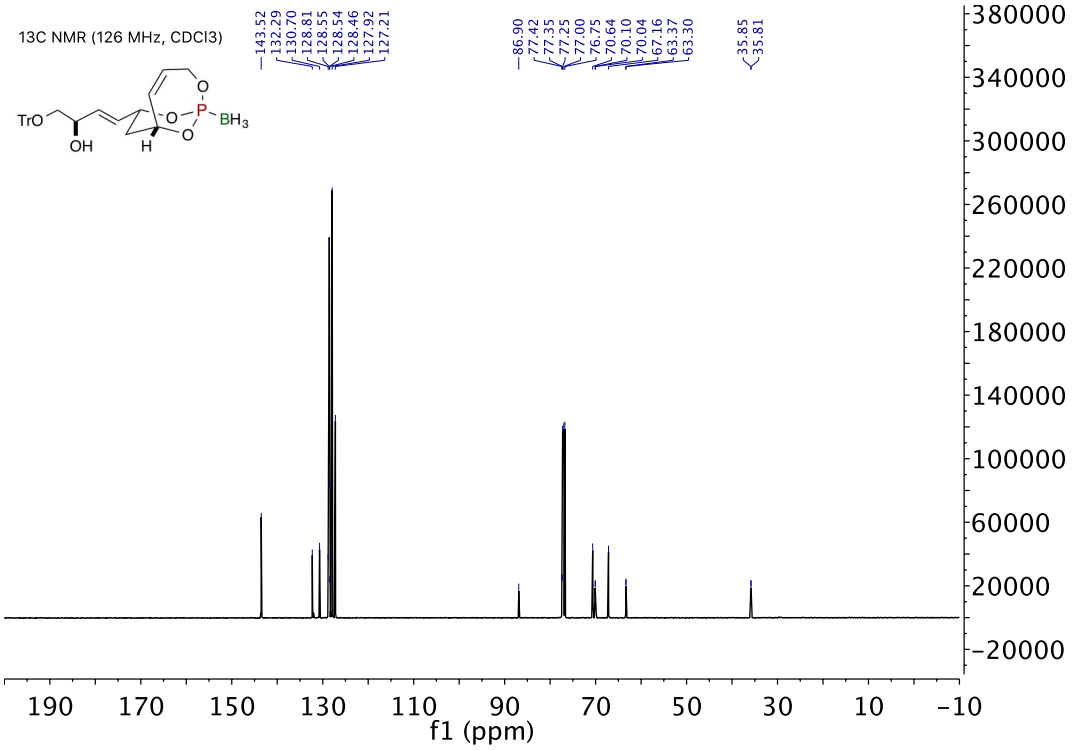

COSY (CDCl3)
EtO
O
O
O
P
BH3
H
f2 (ppm)
f1 (ppm)

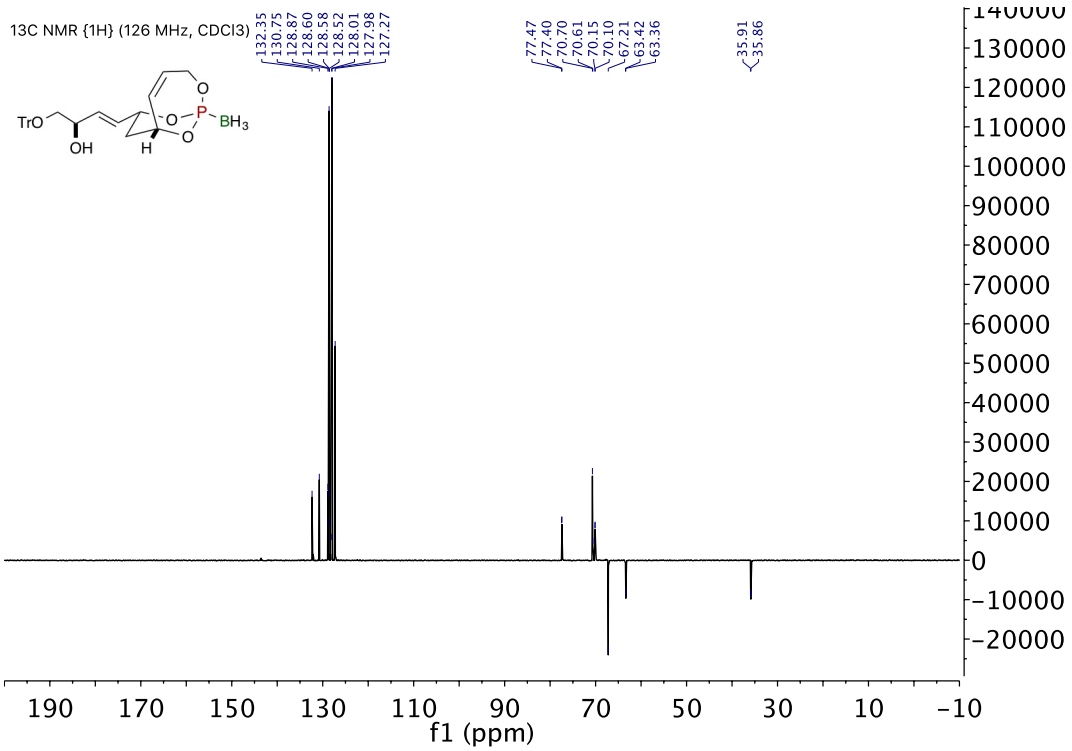

113.81
113.08
31P NMR (162 MHz, CDCl3)
EtO
O
O
O
P
BH3
H
f1 (ppm)

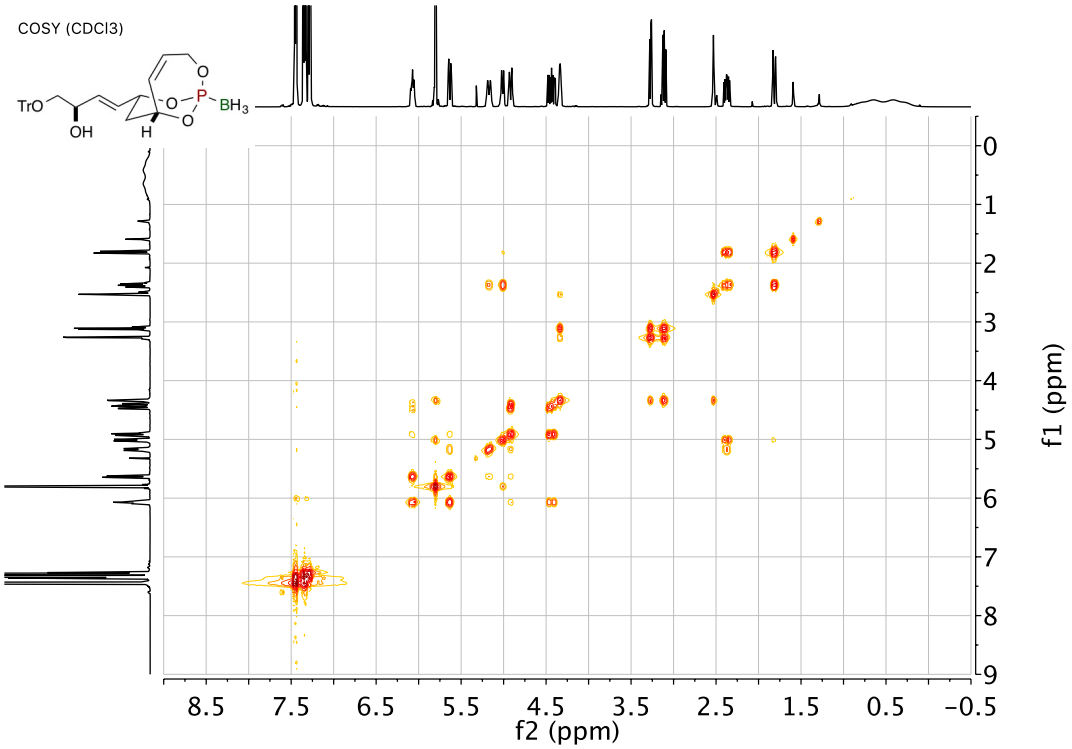

11B NMR (160 MHz, CDCl3)
EtO
O
O
O
O
P
BH3
H
-41.62
-42.24
-42.84
-43.45
-44.05
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
-25
-30
-35
-40
-45
-50
-55
-60
-65
f1 (ppm)

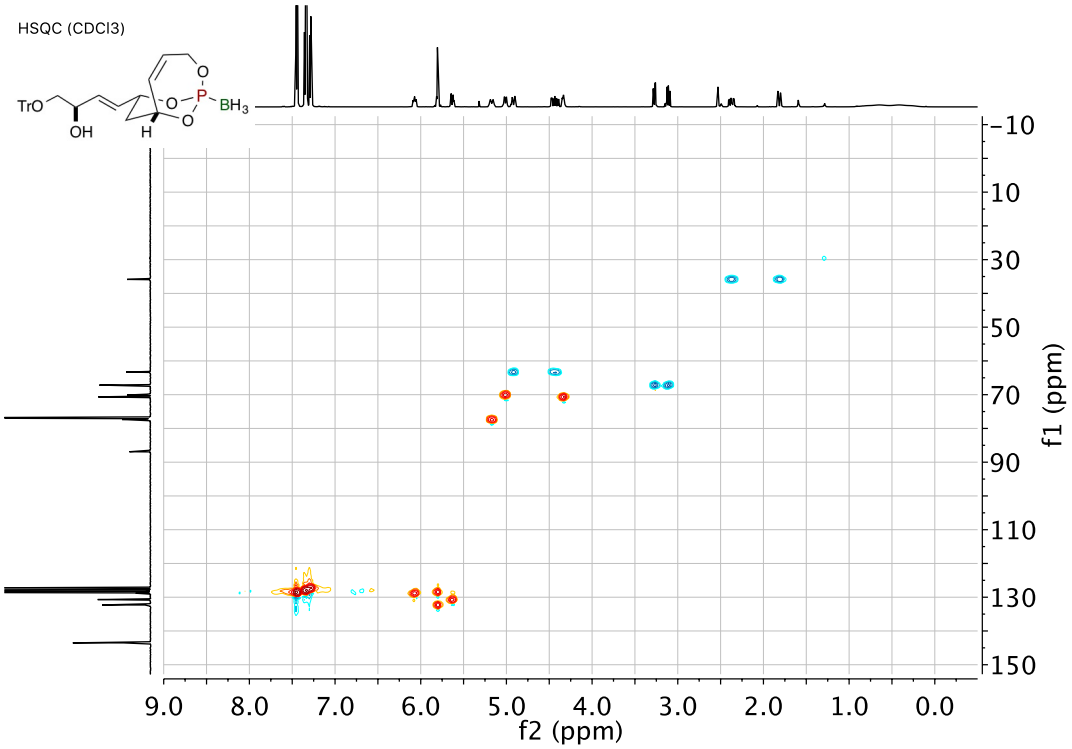
**(*R*,*E*)-4-((1*S*,6*R*,8*R*)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl-1-borane)-1-(trityloxy)but-3-en-2-ol ($C_{29}H_{32}BO_5P$, 3.11.6)**

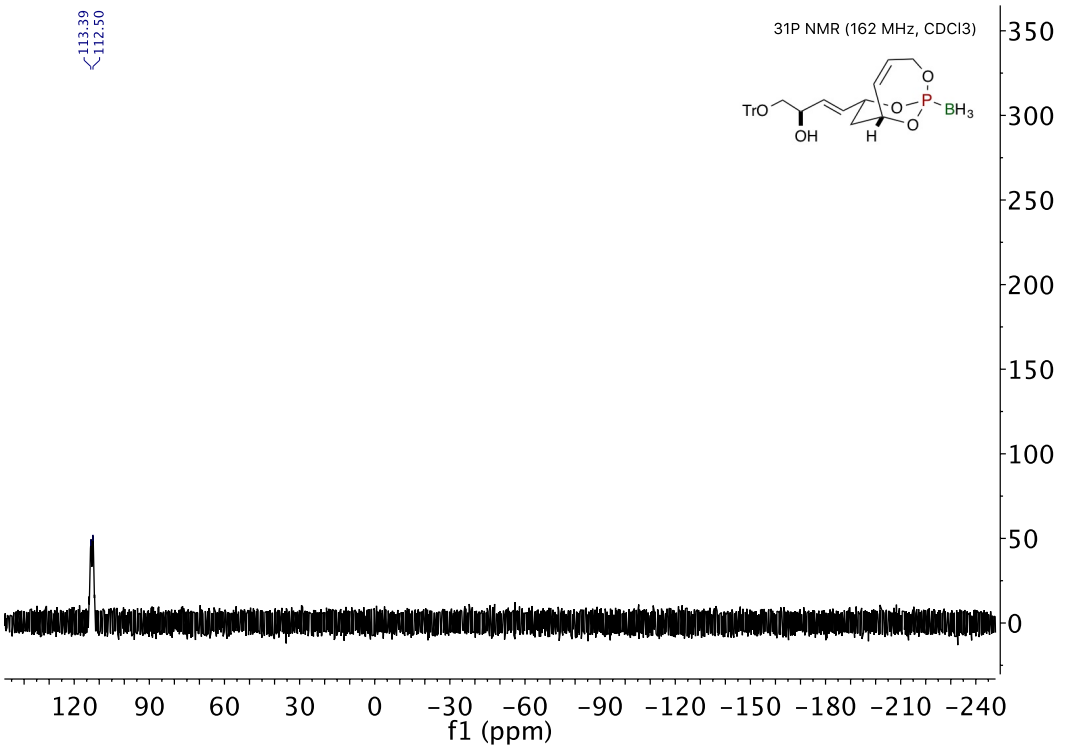


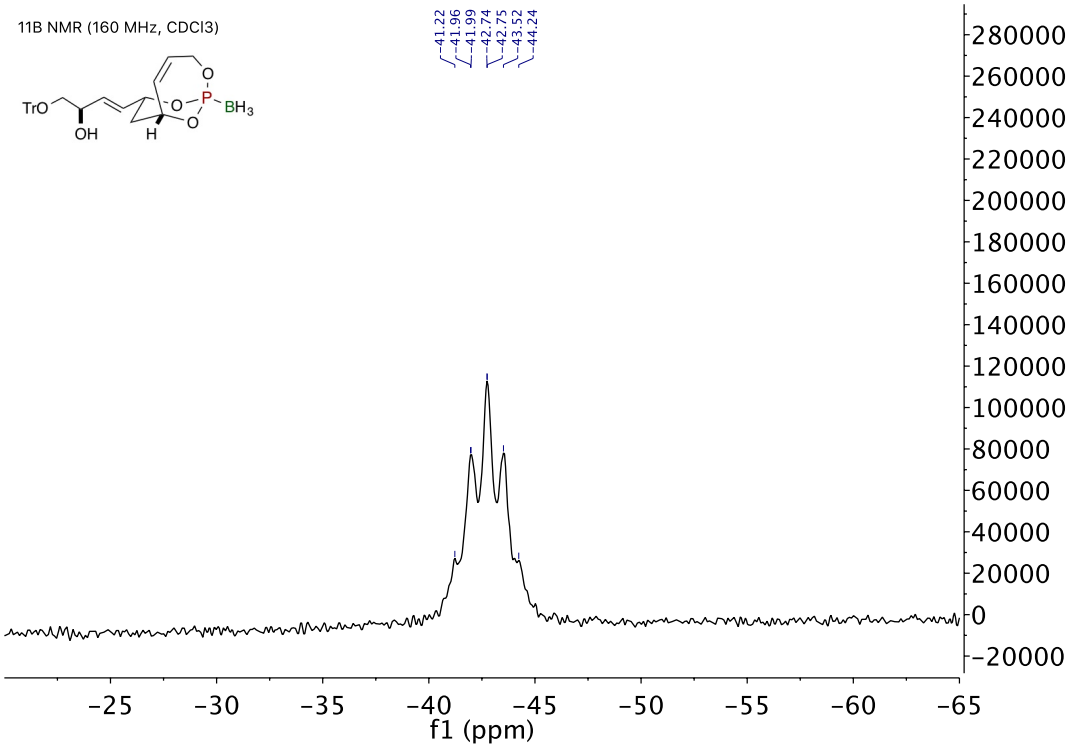

13C NMR (126 MHz, CDCl3)
143.52
132.29
130.70
128.81
128.55
128.54
128.46
127.92
127.21
86.90
77.42
77.35
77.25
77.00
76.75
70.64
70.10
70.04
67.16
63.37
63.30
35.85
35.81
TrO
OH
H
O
P
BH3
380000
340000
300000
260000
220000
180000
140000
100000
60000
20000
-20000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)


13C NMR {1H} (126 MHz, CDCl3)
132.35
130.75
128.87
128.60
128.58
128.52
128.01
127.98
127.27
77.47
77.40
70.70
70.61
70.15
70.10
67.21
63.42
63.36
35.91
35.86
TrO
OH
H
O
P
BH3
130000
120000
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
-20000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

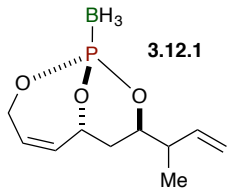

COSY (CDCl3)
TrO
OH
H
O
P
O
O
BH3
0
1
2
3
4
5
6
7
8
9
f1 (ppm)
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f2 (ppm)


HSQC (CDCl3)
TrO
OH
H
O
P
O
O
BH3
-10
10
30
50
70
90
110
130
150
f1 (ppm)
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f2 (ppm)

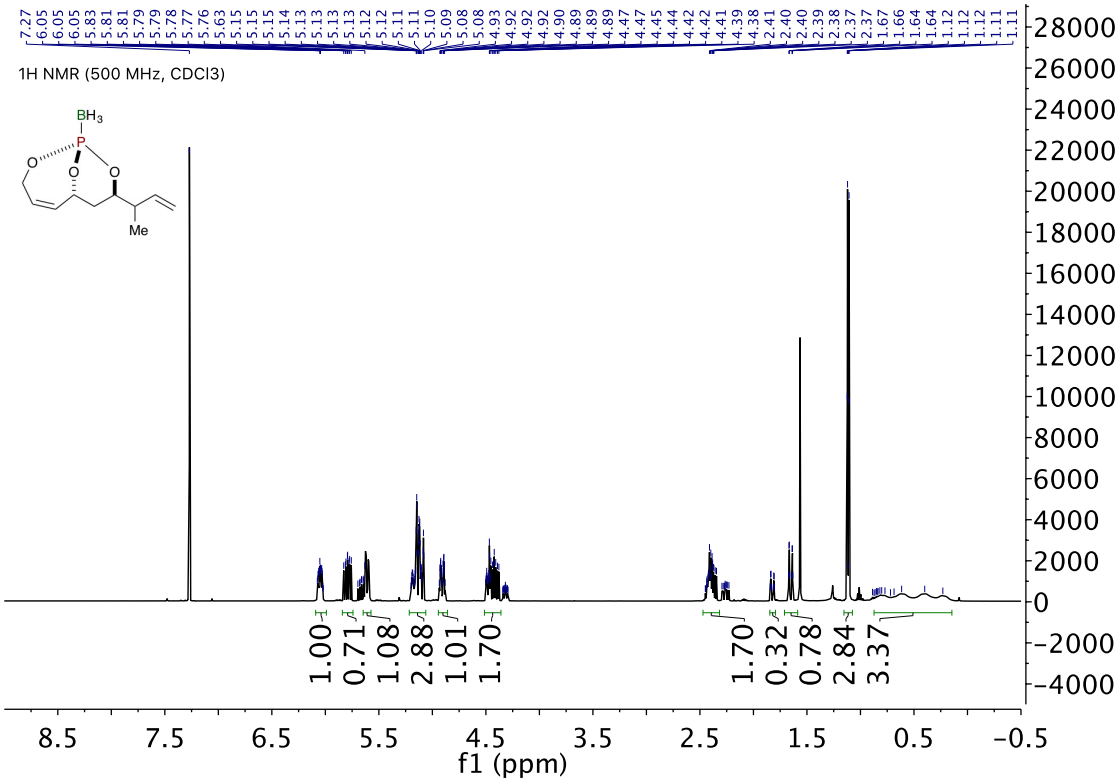

31P NMR (162 MHz, CDCl3)
113.39
112.50
TrO
OH
H
O
P
BH3
350
300
250
200
150
100
50
0
120 90 60 30 0 -30 -60 -90 -120 -150 -180 -210 -240
f1 (ppm)

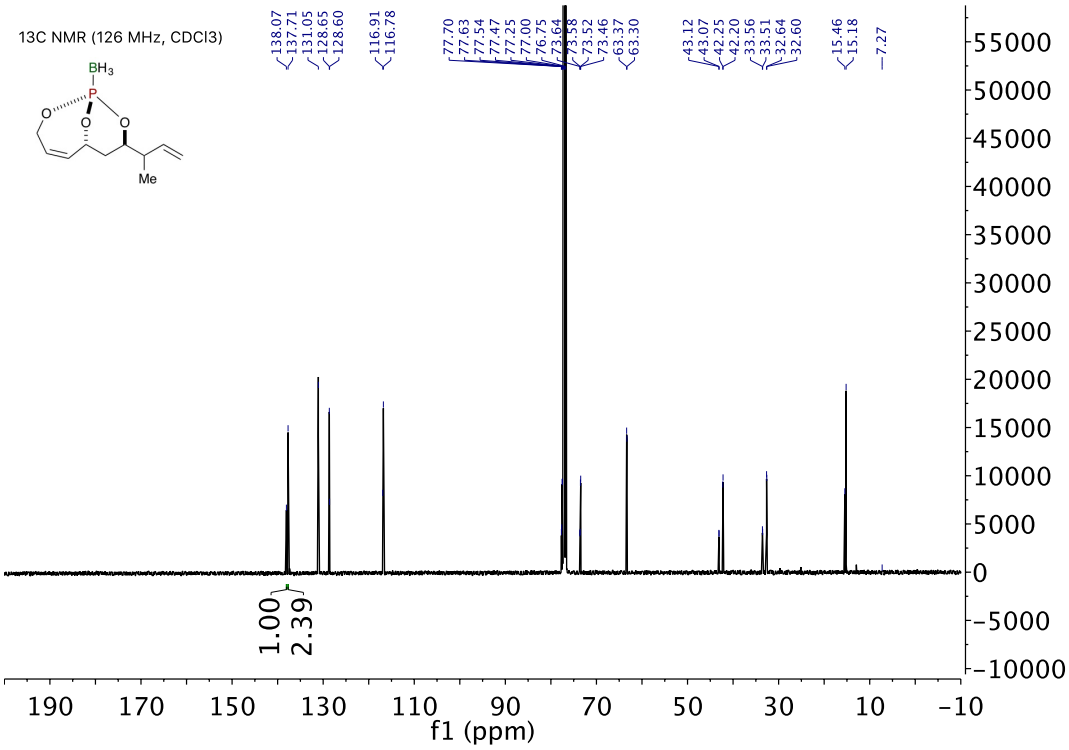

11B NMR (160 MHz, CDCl3)
-41.22
-41.96
-41.99
-42.74
-42.75
-43.52
-44.24
TrO
OH
H
O
P
BH3
280000
260000
240000
220000
200000
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
-20000
-25 -30 -35 -40 -45 -50 -55 -60 -65
f1 (ppm)

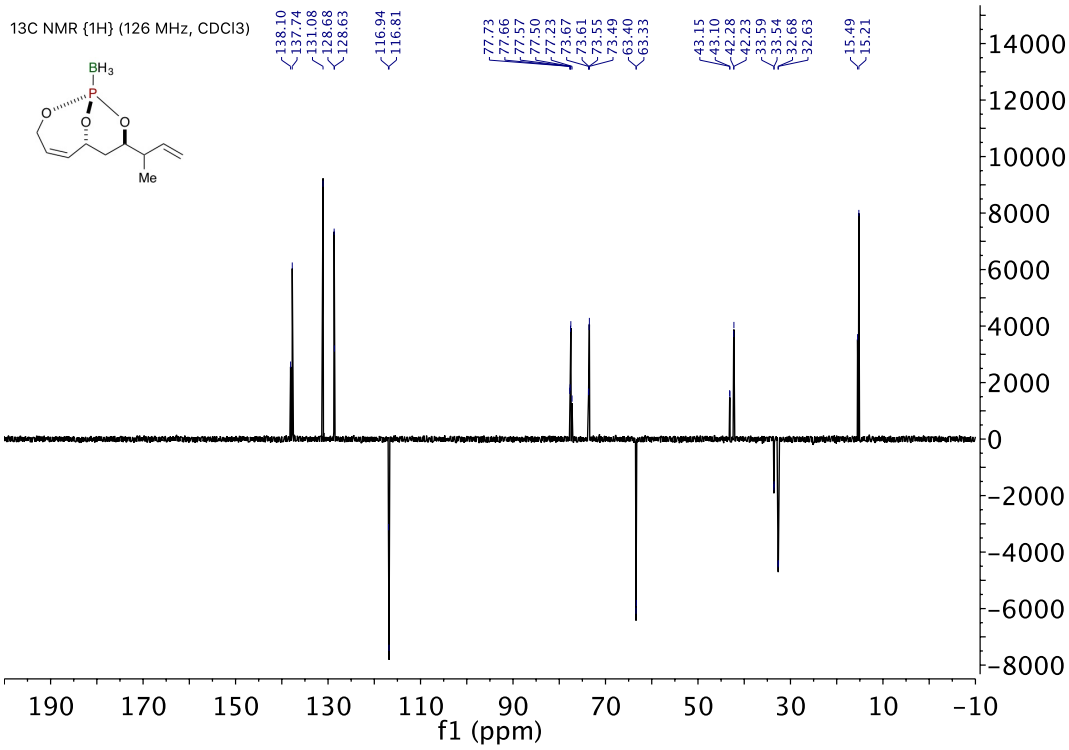
**(1*R*,6*R*,8*R*)-8-(but-3-en-2-yl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene ($C_{10}H_{18}BO_3P$, 3.12.1)**

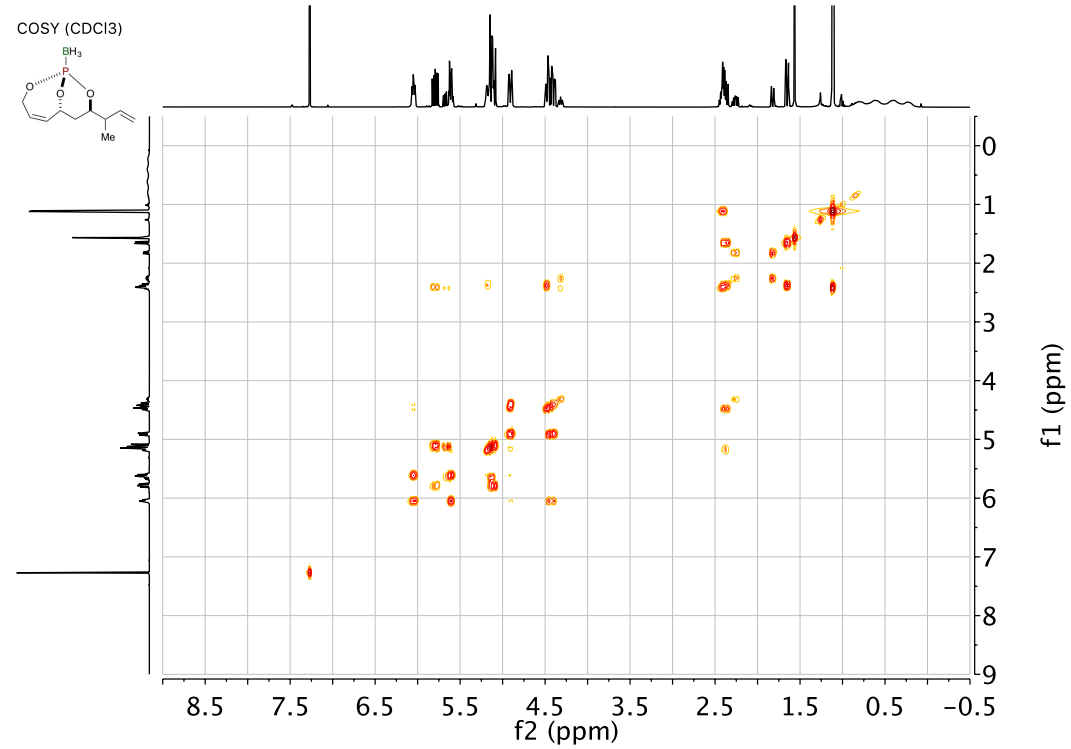


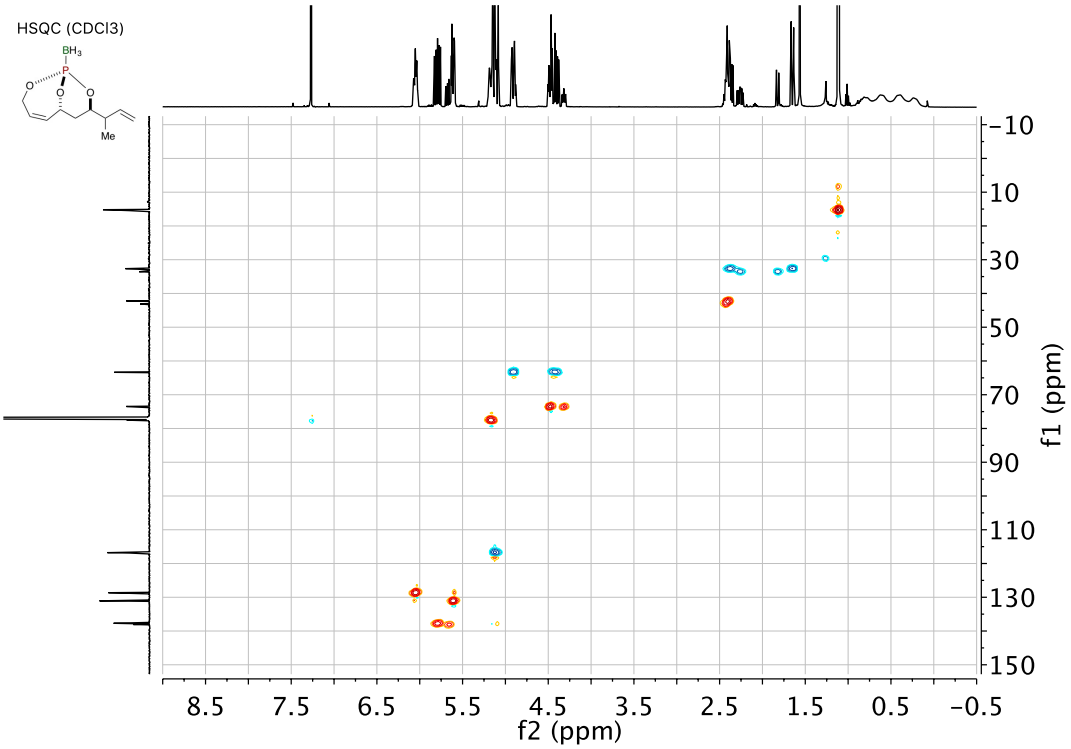

3.12.1

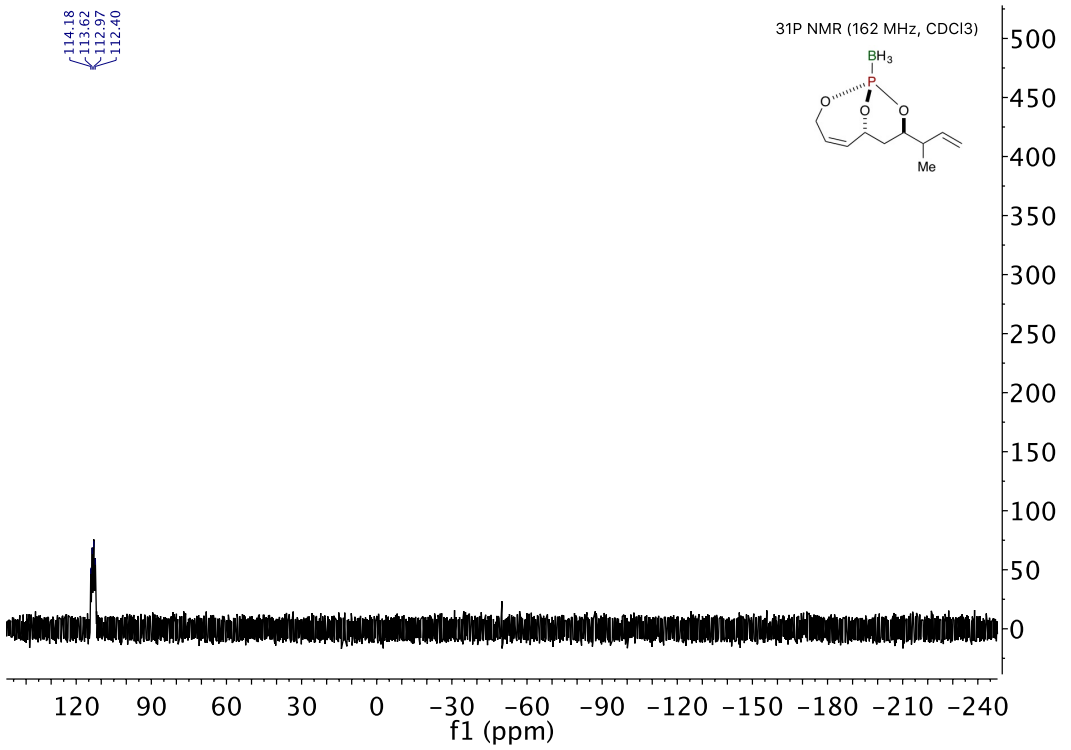


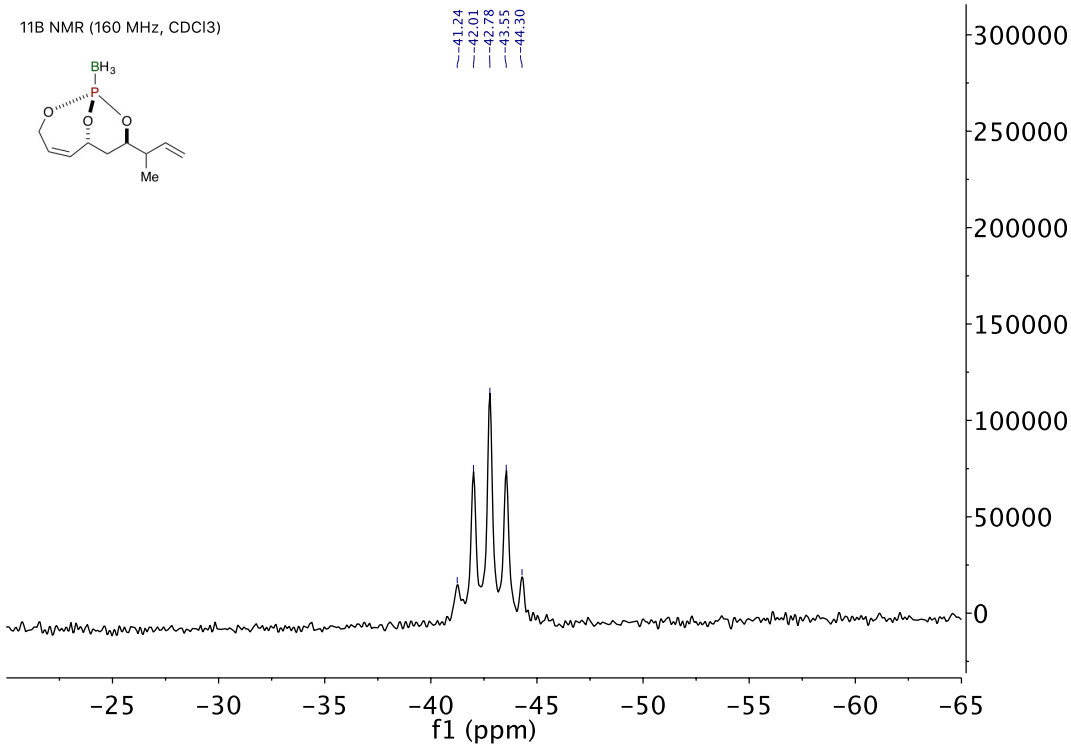

13C NMR (126 MHz, CDCl3)
BH3
P
O
O
O
Me
138.07
137.71
131.05
128.65
128.60
116.91
116.78
77.70
77.63
77.54
77.47
77.25
77.00
76.75
73.64
73.58
73.52
73.46
63.37
63.30
43.12
43.07
42.25
42.20
33.56
33.51
32.64
32.60
15.46
15.18
7.27
1.00
2.39
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
-10000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)


13C NMR {1H} (126 MHz, CDCl3)
BH3
P
O
O
O
Me
138.10
137.74
131.08
128.68
128.63
116.94
116.81
77.73
77.66
77.57
77.50
77.23
73.67
73.61
73.55
73.49
63.40
63.33
43.15
43.10
42.28
42.23
33.59
33.54
32.68
32.63
15.49
15.21
14000
12000
10000
8000
6000
4000
2000
0
-2000
-4000
-6000
-8000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

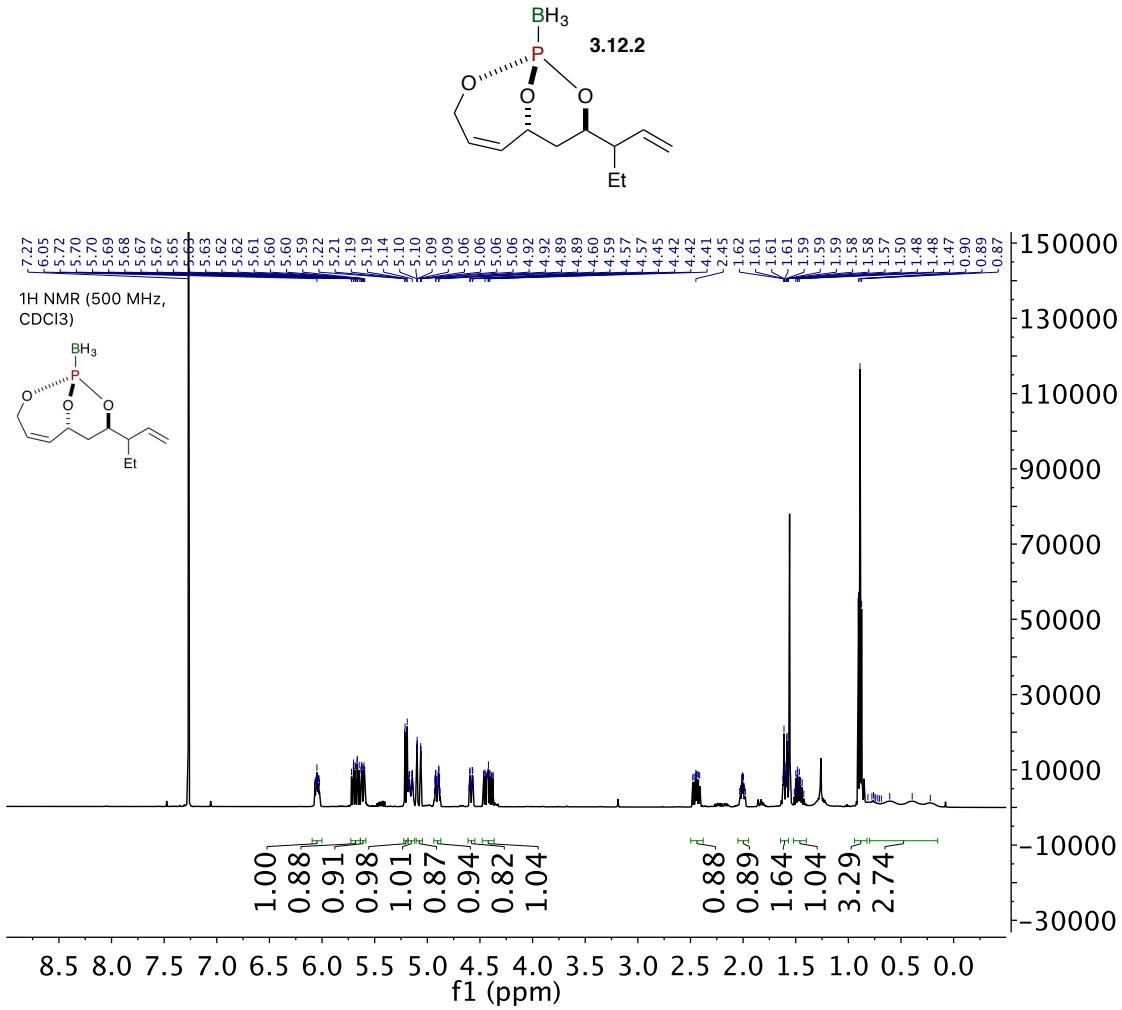

COSY (CDCl3)
BH3
Me
0
1
2
3
4
5
6
7
8
9
f1 (ppm)
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f2 (ppm)

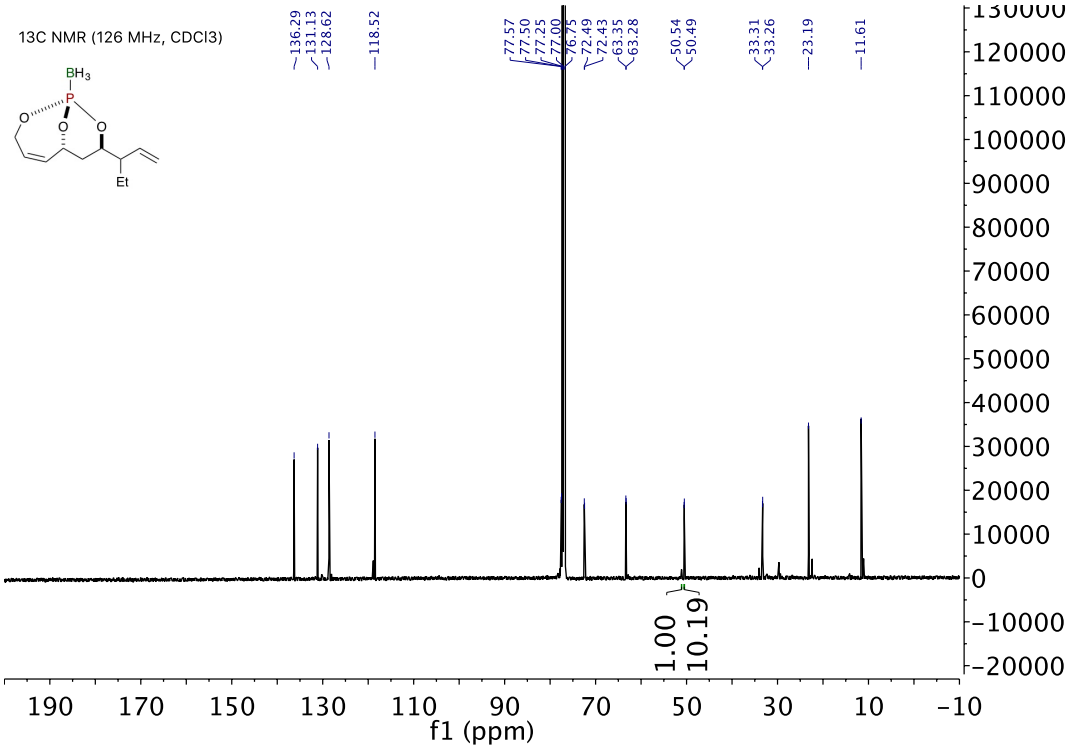

HSQC (CDCl3)
BH3
Me
-10
10
30
50
70
90
110
130
150
f1 (ppm)
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f2 (ppm)

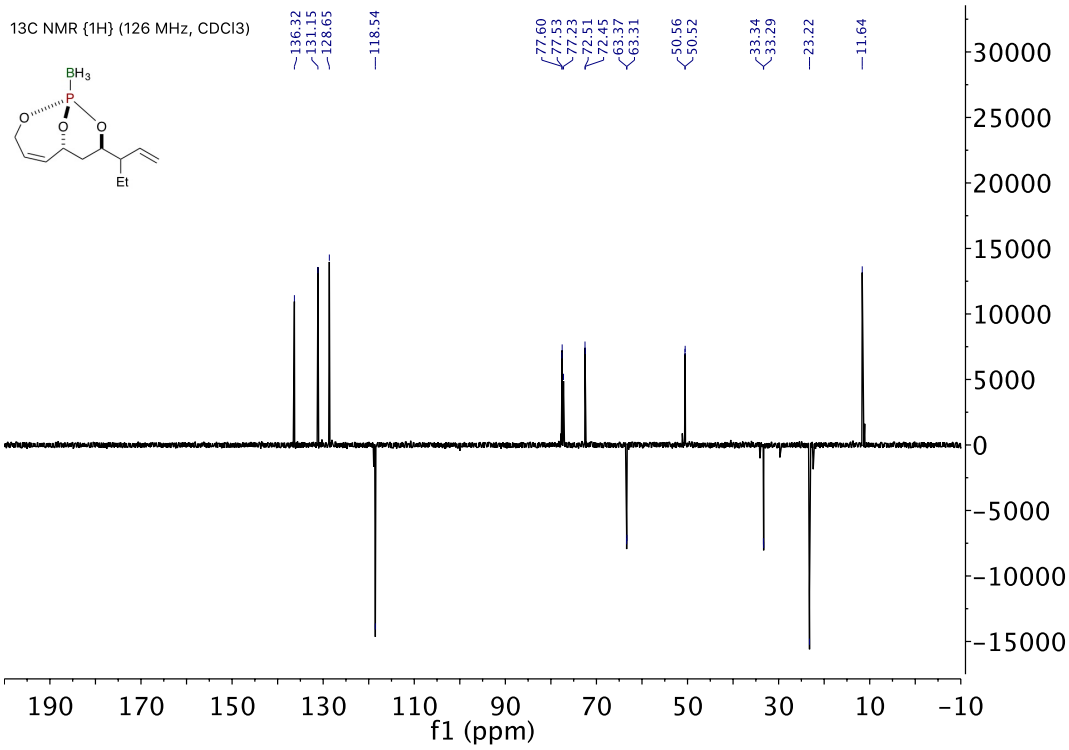

114.18
113.62
112.97
112.40
31P NMR (162 MHz, CDCl3)
BH3
P
O
O
O
Me
500
450
400
350
300
250
200
150
100
50
0
120
90
60
30
0
-30
-60
-90
-120
-150
-180
-210
-240
f1 (ppm)

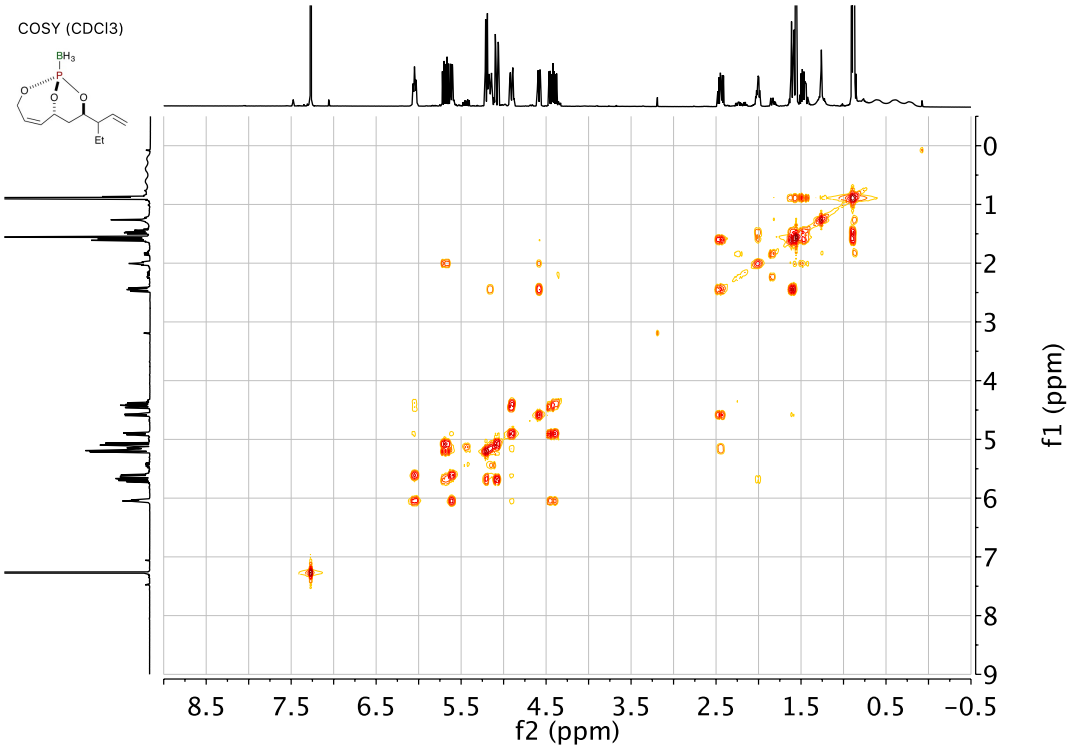

11B NMR (160 MHz, CDCl3)
BH3
P
O
O
O
Me
-41.24
-42.01
-42.78
-43.55
-44.30
300000
250000
200000
150000
100000
50000
0
-25
-30
-35
-40
-45
-50
-55
-60
-65
f1 (ppm)

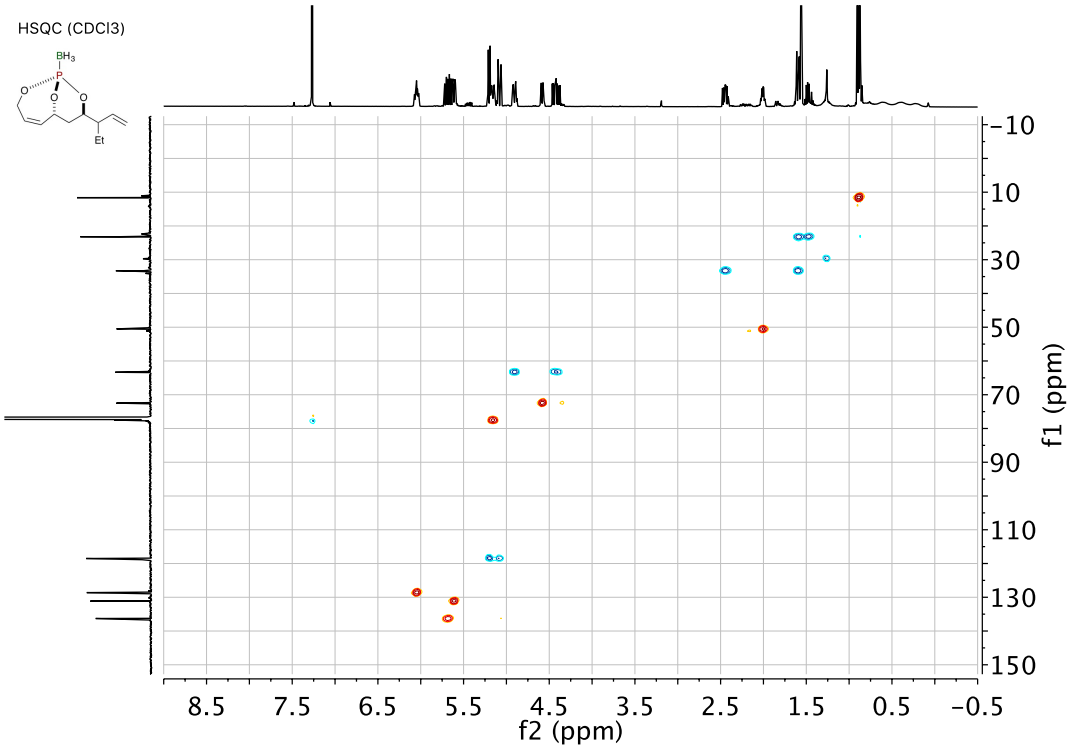
**(1*R*,6*R*,8*R*)-8-(pent-1-en-3-yl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-borane ($C_{11}H_{20}BO_3P$, 3.12.2)**

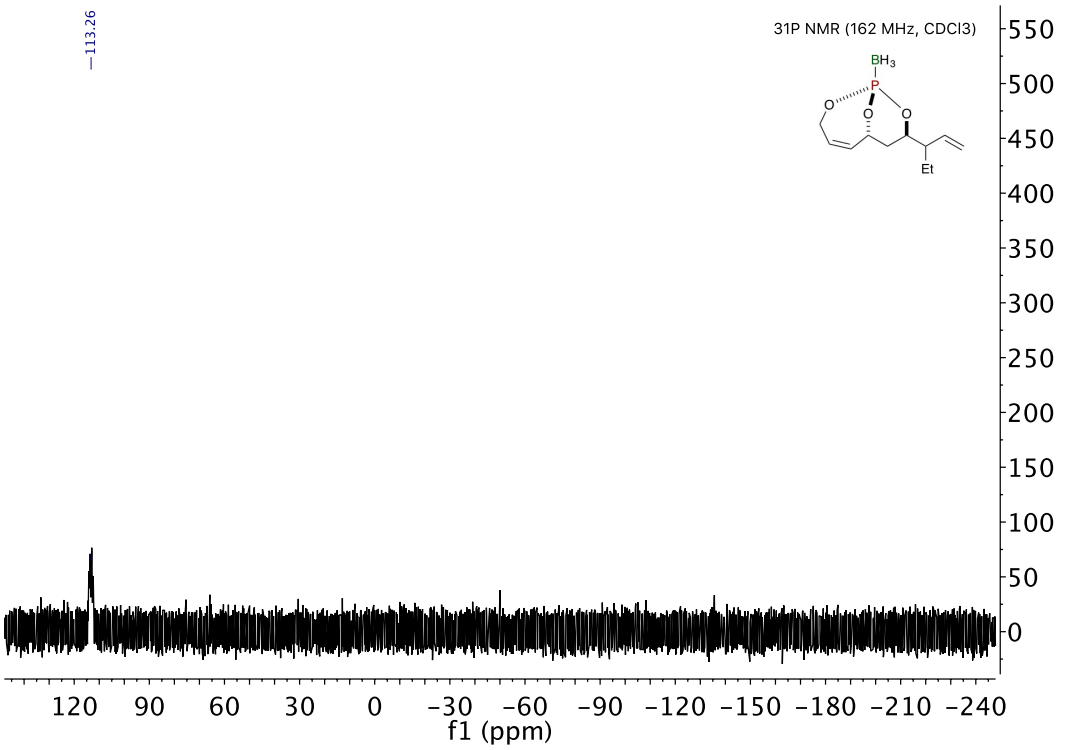


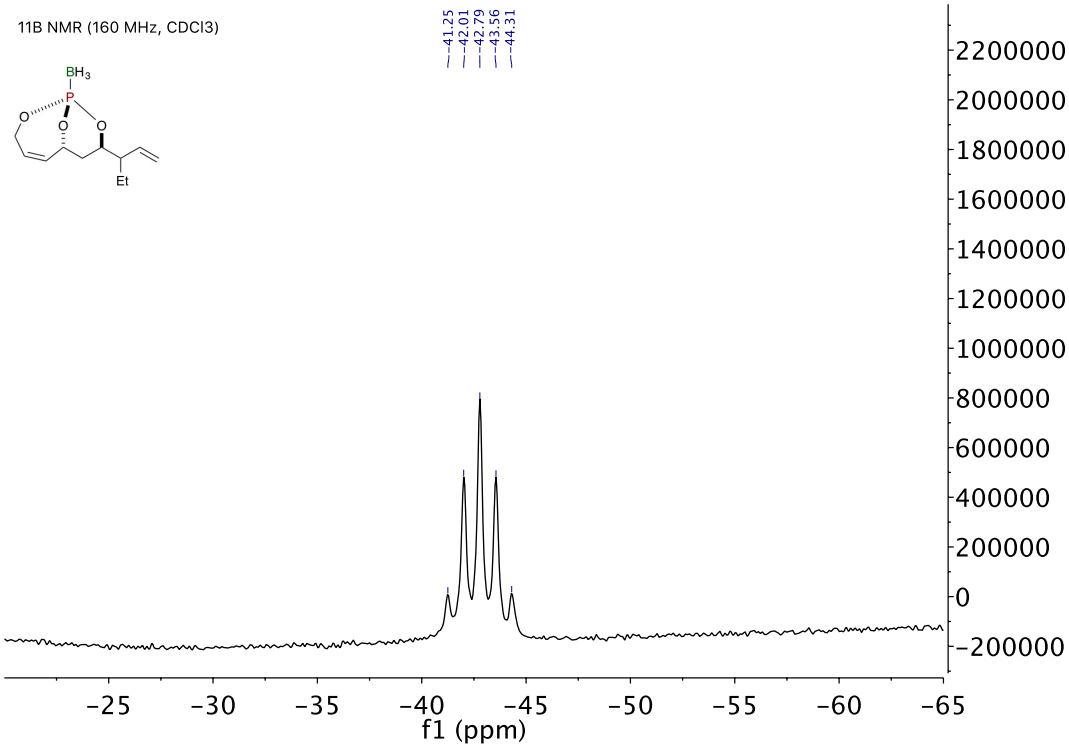

13C NMR (126 MHz, CDCl3)
BH3
P
O
O
O
Et
136.29
131.13
128.62
118.52
77.57
77.50
77.25
77.00
76.75
72.49
72.43
63.35
63.28
50.54
50.49
33.31
33.26
23.19
11.61
1.00
10.19
f1 (ppm)


13C NMR {1H} (126 MHz, CDCl3)
BH3
P
O
O
O
Et
136.32
131.15
128.65
118.54
77.60
77.53
77.23
72.51
72.45
63.37
63.31
50.56
50.52
33.34
33.29
23.22
11.64
f1 (ppm)

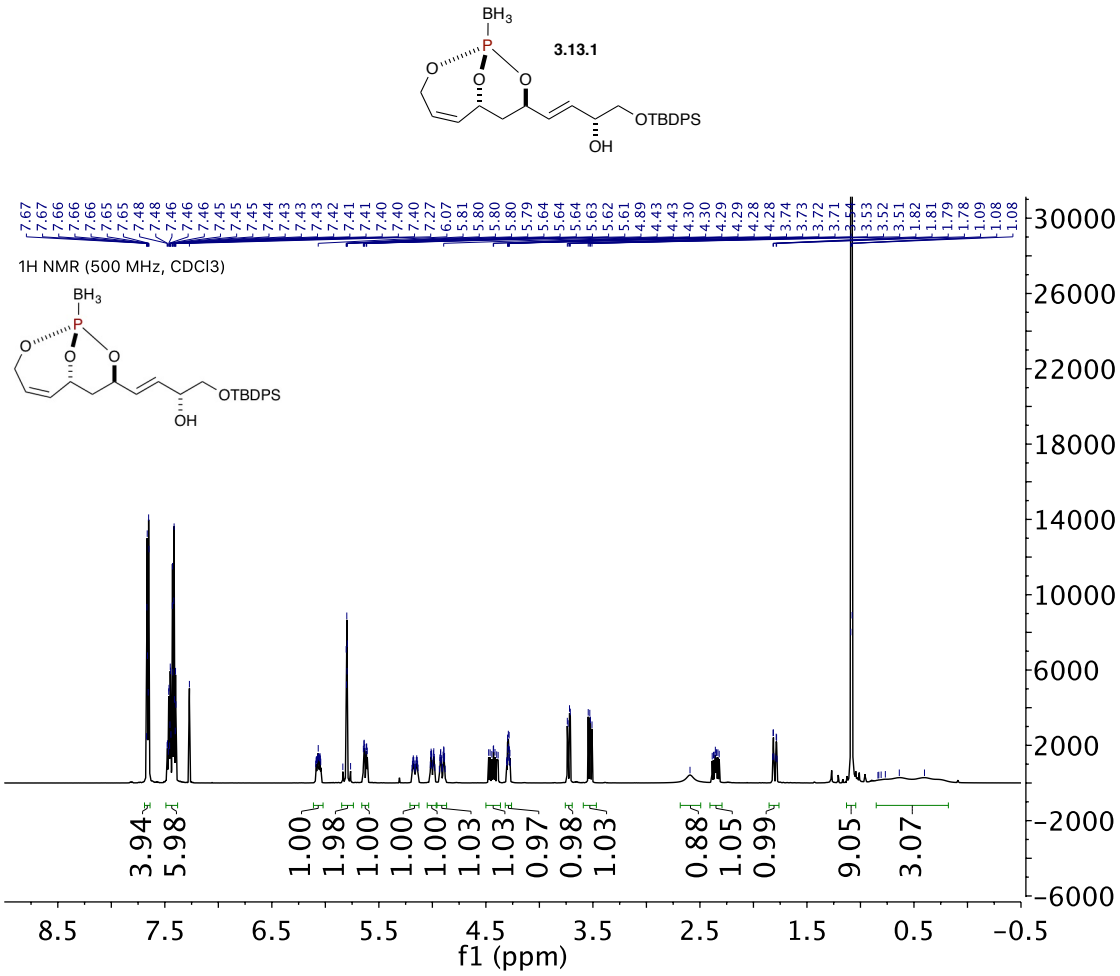

COSY (CDCl3)
BH3
P
O
O
O
Et
0
1
2
3
4
5
6
7
8
9
f1 (ppm)
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f2 (ppm)

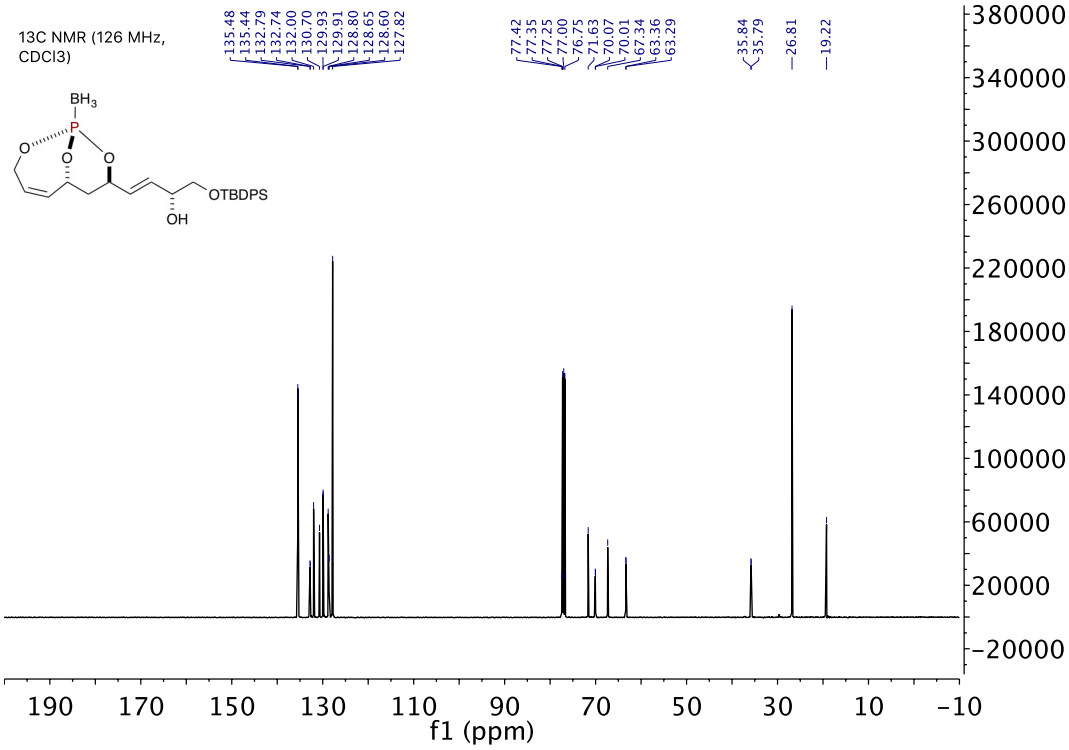

HSQC (CDCl3)
BH3
P
O
O
O
Et
-10
10
30
50
70
90
110
130
150
f1 (ppm)
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f2 (ppm)

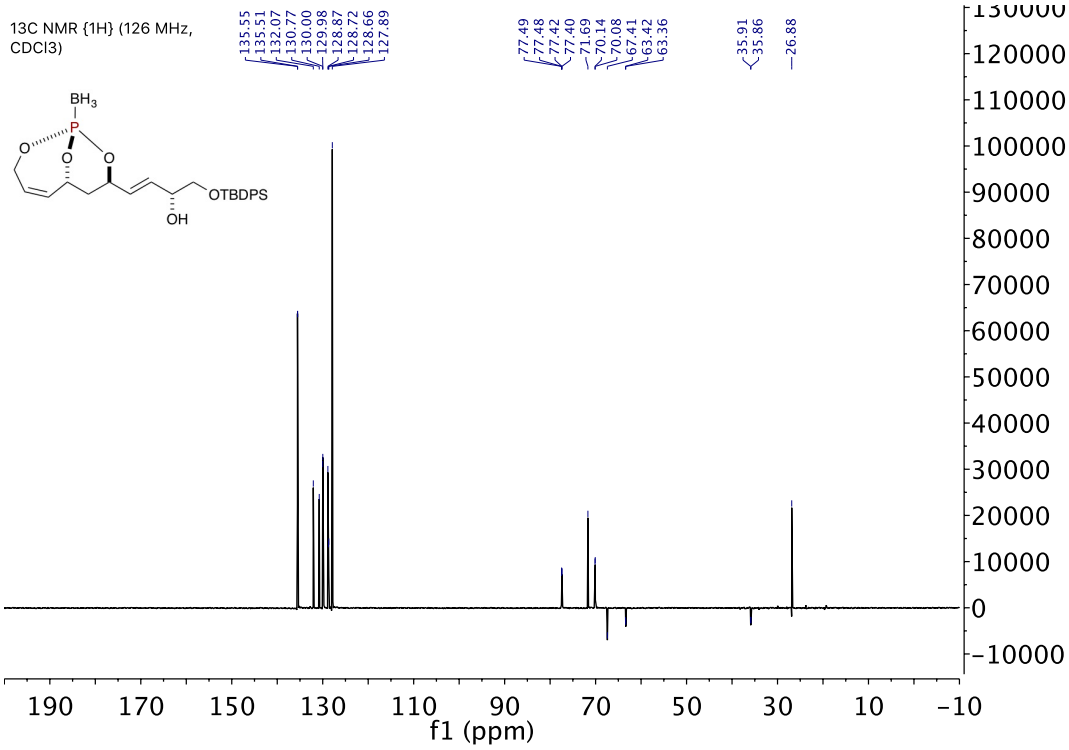

31P NMR (162 MHz, CDCl3)
113.26
550
500
450
400
350
300
250
200
150
100
50
0
120 90 60 30 0 -30 -60 -90 -120 -150 -180 -210 -240
f1 (ppm)

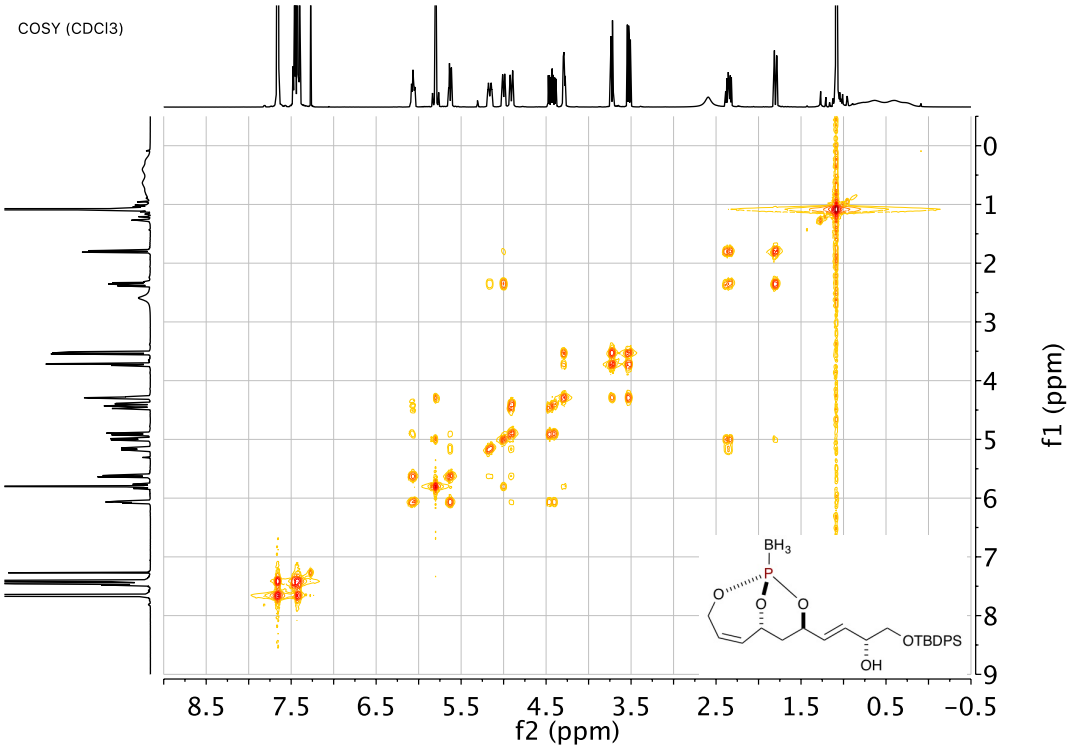

11B NMR (160 MHz, CDCl3)
41.25
42.01
42.79
43.56
44.31
2200000
2000000
1800000
1600000
1400000
1200000
1000000
800000
600000
400000
200000
0
-200000
-25 -30 -35 -40 -45 -50 -55 -60 -65
f1 (ppm)

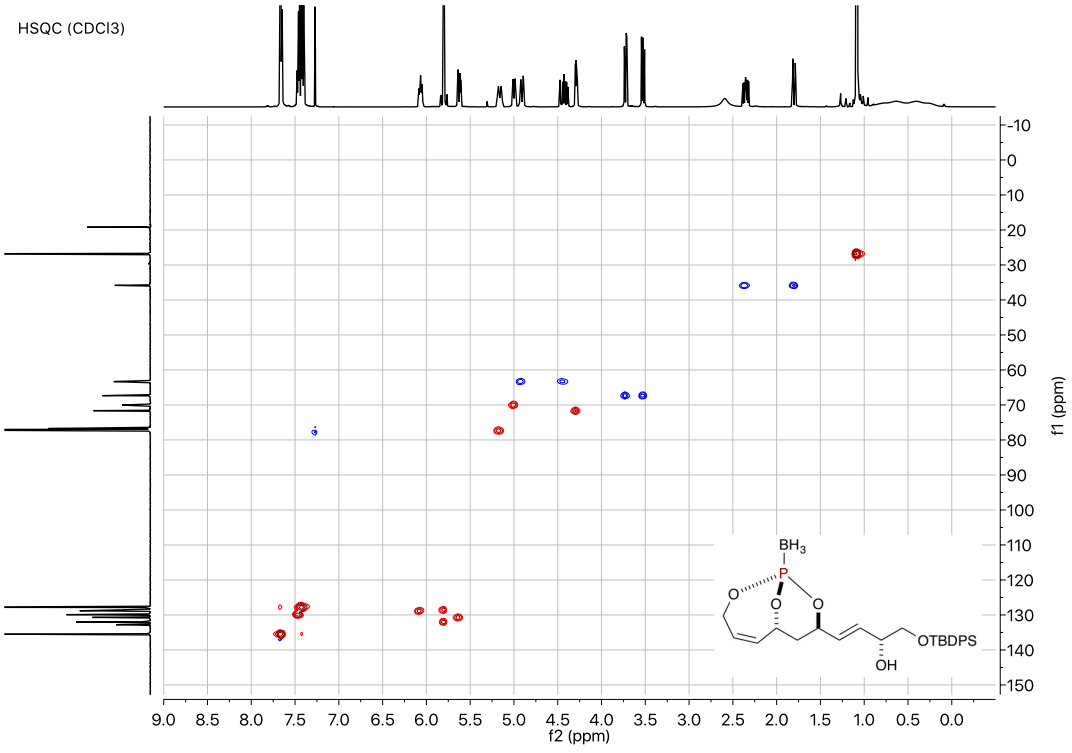
**(*R*,*E*)-4-((1*S*,6*R*,8*R*)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl-1-borane)-1-((*tert*-butyldiphenylsilyl)oxy)but-3-en-2-ol ($C_{26}H_{36}BO_5PSi$, 3.13.1)**

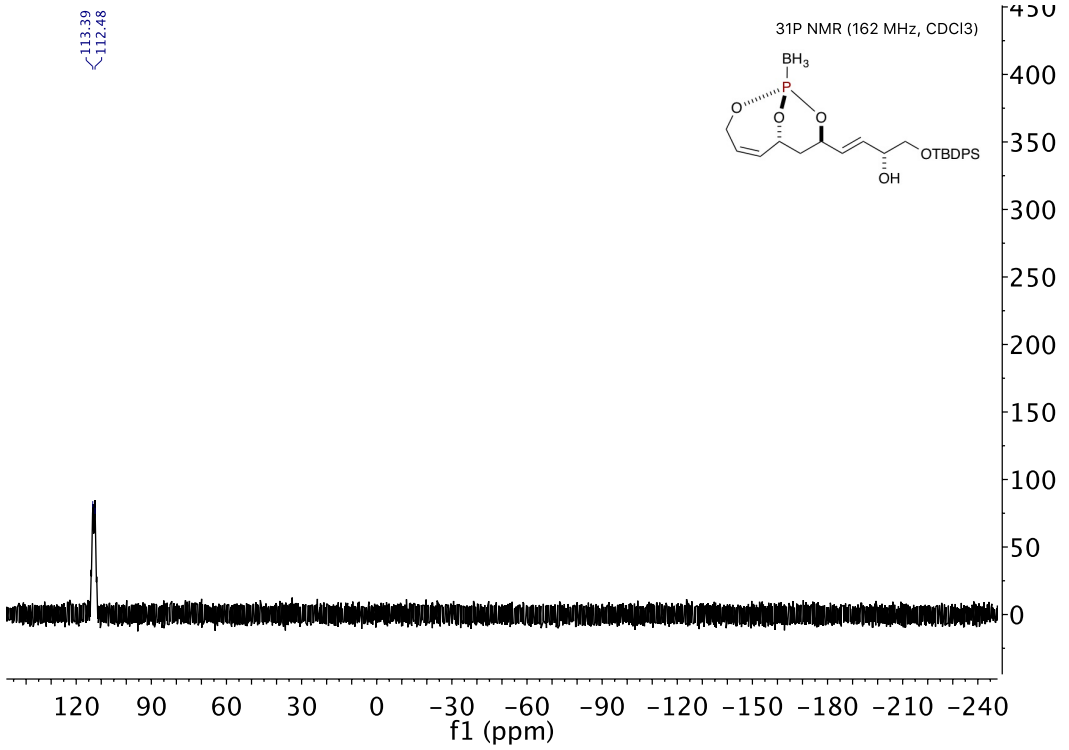


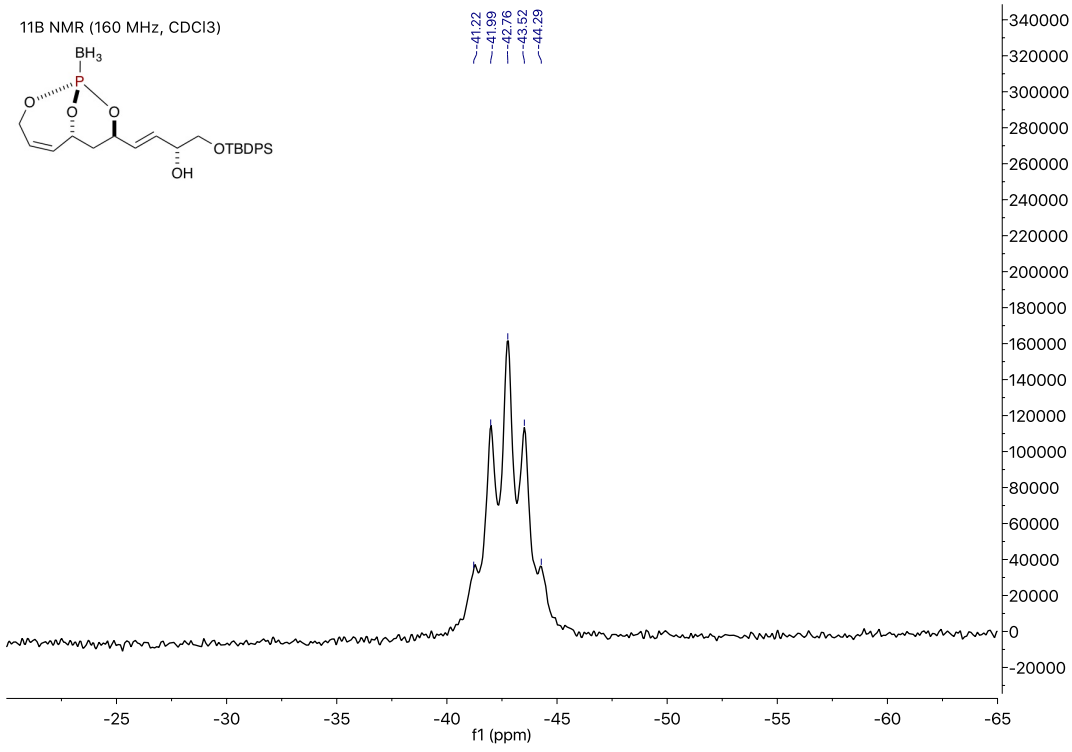

13C NMR (126 MHz, CDCl3)
135.48
135.44
132.79
132.74
132.00
130.70
129.93
129.91
128.80
128.65
128.60
127.82
77.42
77.35
77.25
77.00
76.75
71.63
70.07
70.01
67.34
63.36
63.29
35.84
35.79
26.81
19.22
BH3
P
O
O
O
OTBDPS
OH
380000
340000
300000
260000
220000
180000
140000
100000
60000
20000
-20000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)


13C NMR {1H} (126 MHz, CDCl3)
135.55
135.51
132.07
130.77
130.00
129.98
128.87
128.72
128.66
127.89
77.49
77.48
77.42
77.40
71.69
70.14
70.08
67.41
63.42
63.36
35.91
35.86
26.88
BH3
P
O
O
O
OTBDPS
OH
130000
120000
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

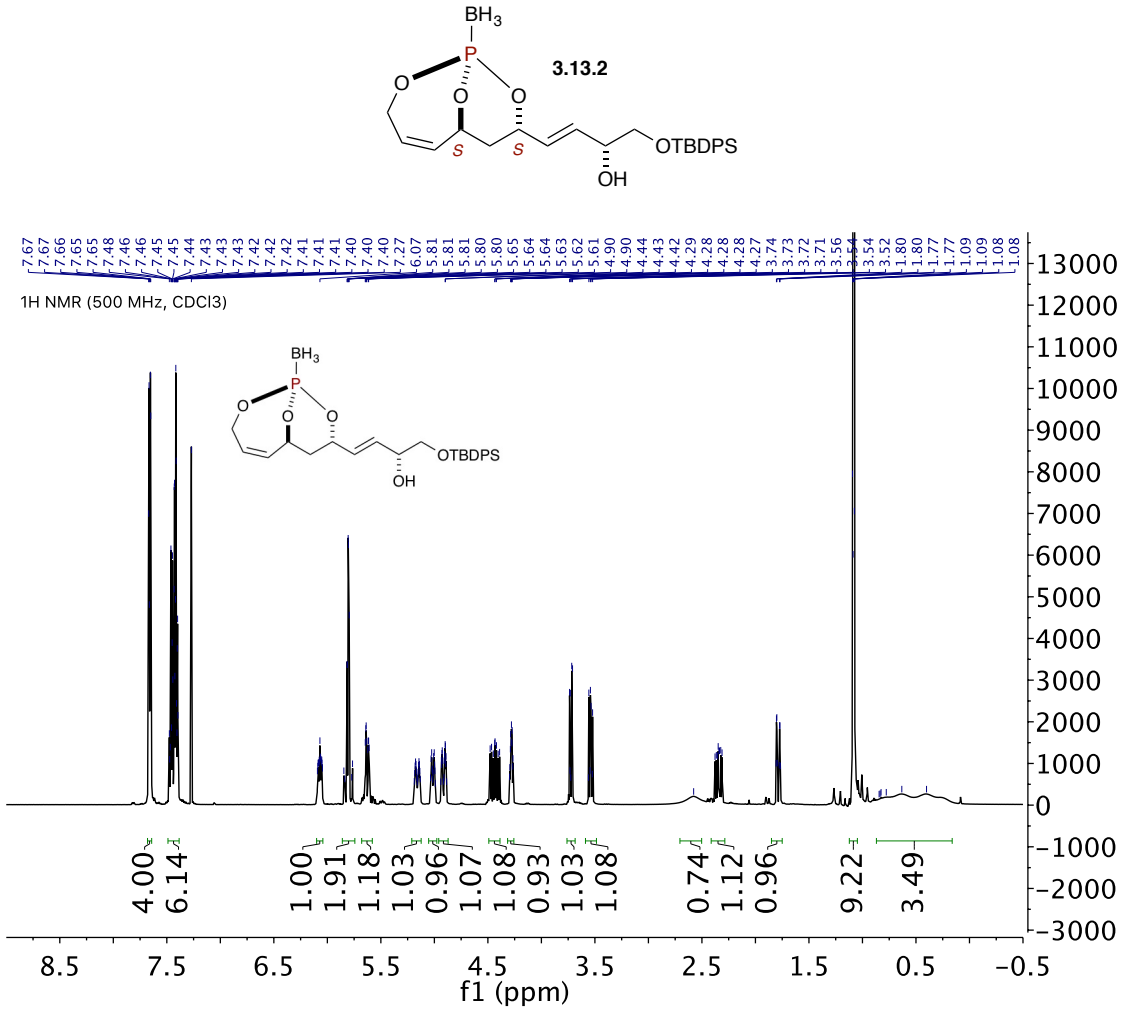

COSY (CDCl3)
f1 (ppm)
f2 (ppm)
BH3
OTBDPS
OH

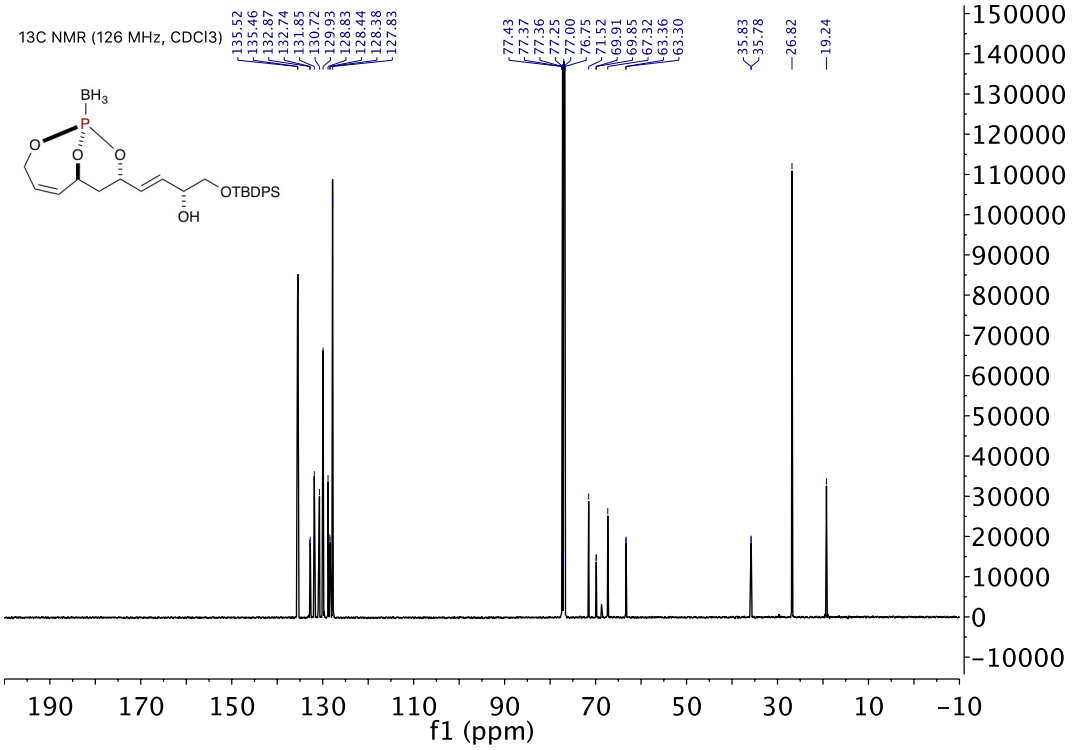

HSQC (CDCl3)
f1 (ppm)
f2 (ppm)
BH3
OTBDPS
OH

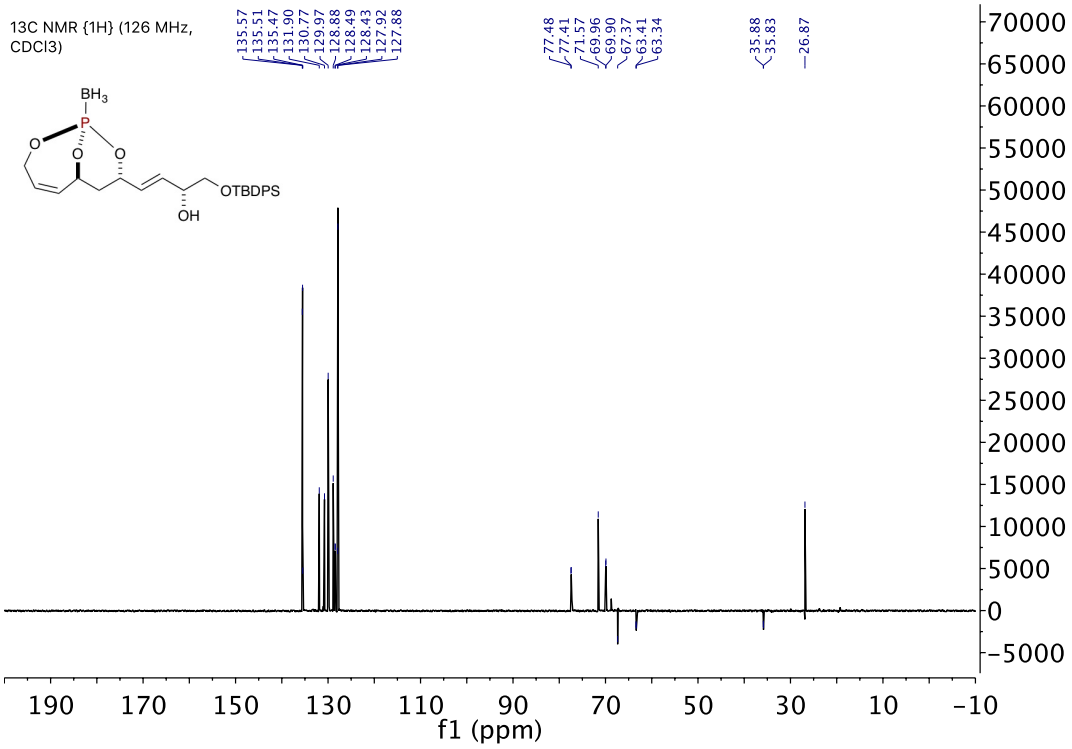

113.39
112.48
31P NMR (162 MHz, CDCl3)
BH3
P
O
O
O
OTBDPS
OH
450
400
350
300
250
200
150
100
50
0
120 90 60 30 0 -30 -60 -90 -120 -150 -180 -210 -240
f1 (ppm)

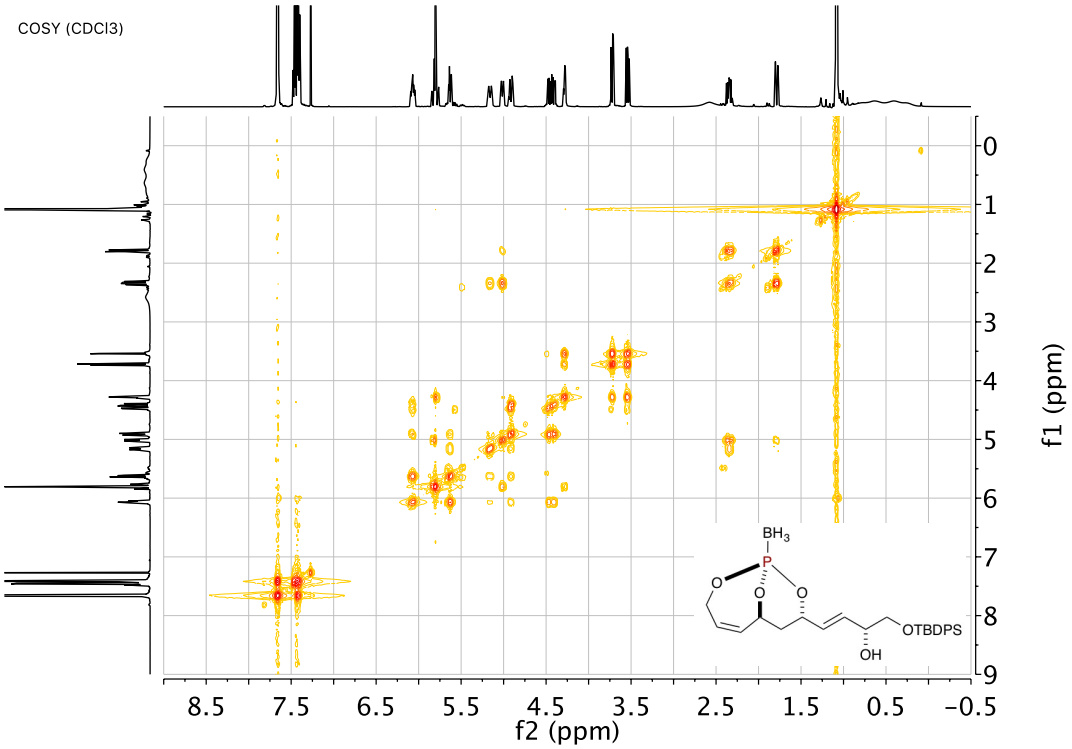

11B NMR (160 MHz, CDCl3)
BH3
P
O
O
O
OTBDPS
OH
41.22
41.99
42.76
43.52
44.29
340000
320000
300000
280000
260000
240000
220000
200000
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
-20000
-25 -30 -35 -40 -45 -50 -55 -60 -65
f1 (ppm)

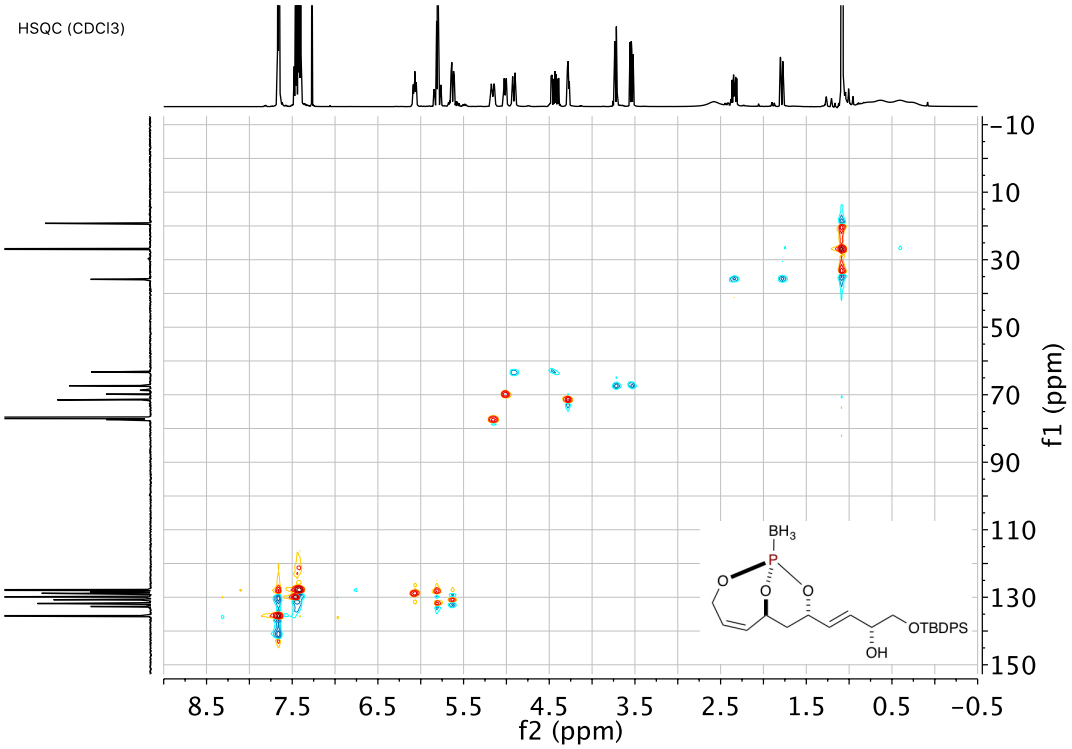
**(*R*,*E*)-4-((1*R*,6*S*,8*S*)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl-1-borane)-1-((*tert*-butyldiphenylsilyl)oxy)but-3-en-2-ol ($C_{26}H_{36}BO_5PSi$, 3.13.2)**

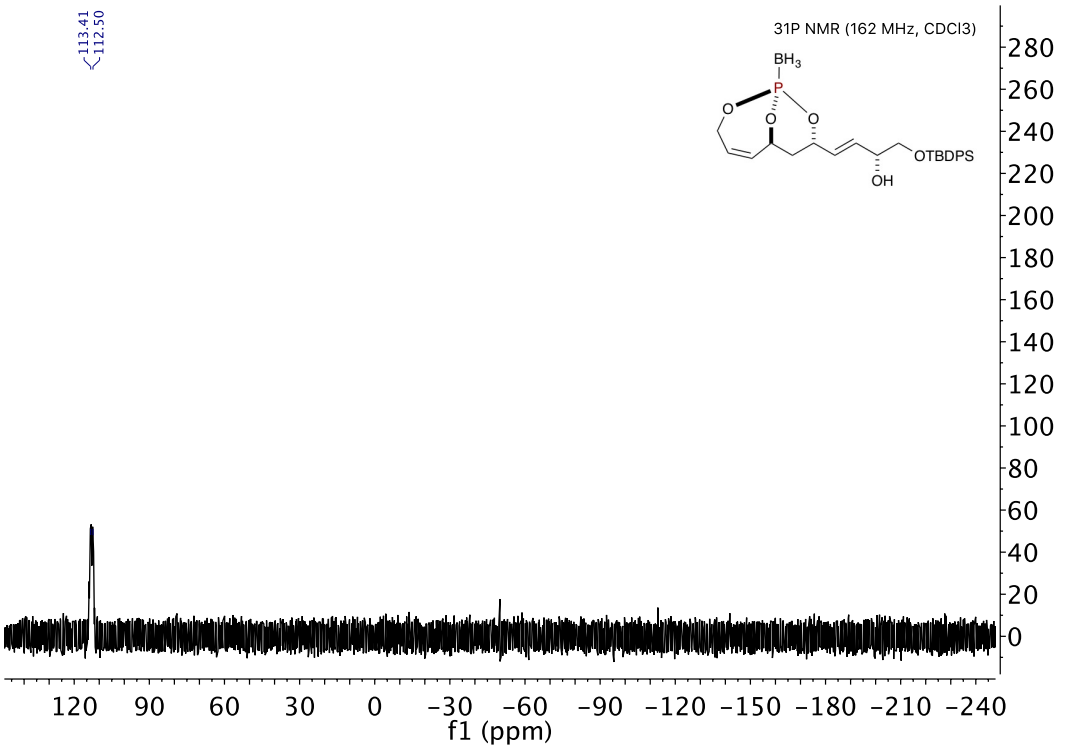


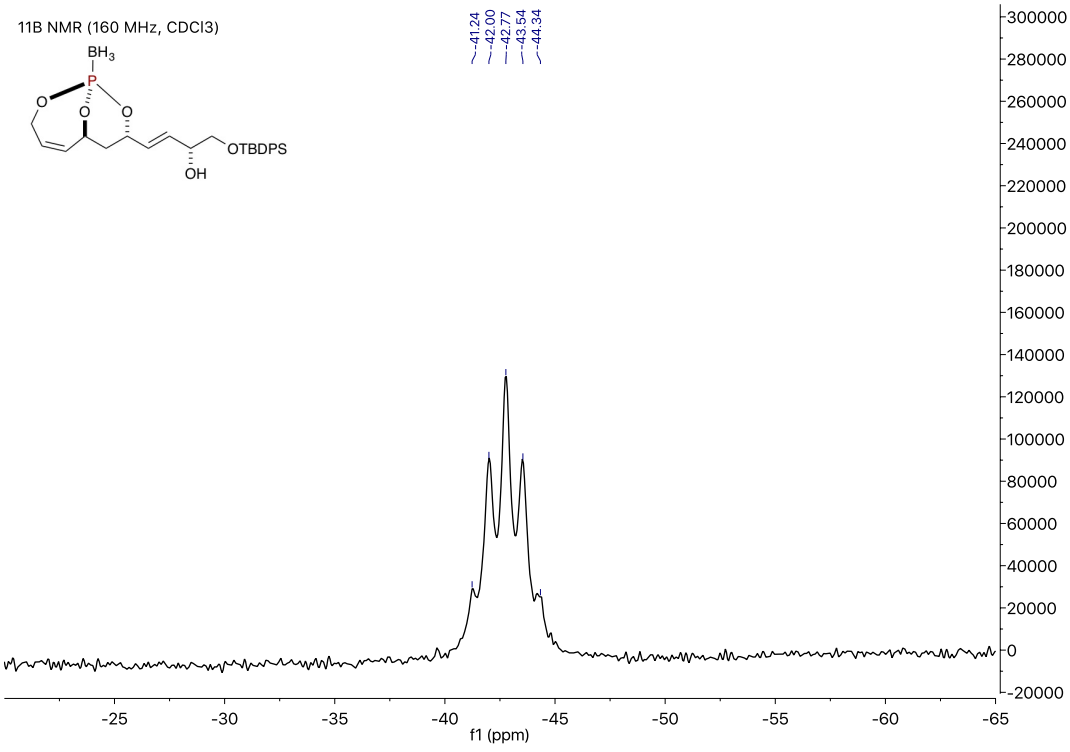

13C NMR (126 MHz, CDCl3)
135.52
135.46
132.87
132.74
131.85
130.72
129.93
128.83
128.44
128.38
127.83
77.43
77.37
77.36
77.25
77.00
76.75
71.52
69.91
69.85
67.32
63.36
63.30
35.83
35.78
26.82
19.24
BH3
P
O
O
O
OTBDPS
OH
150000
140000
130000
120000
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)


13C NMR {1H} (126 MHz, CDCl3)
135.57
135.51
135.47
131.90
130.77
129.97
128.88
128.49
128.43
127.92
127.88
77.48
77.41
71.57
69.96
69.90
67.37
63.41
63.34
35.88
35.83
26.87
BH3
P
O
O
O
OTBDPS
OH
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

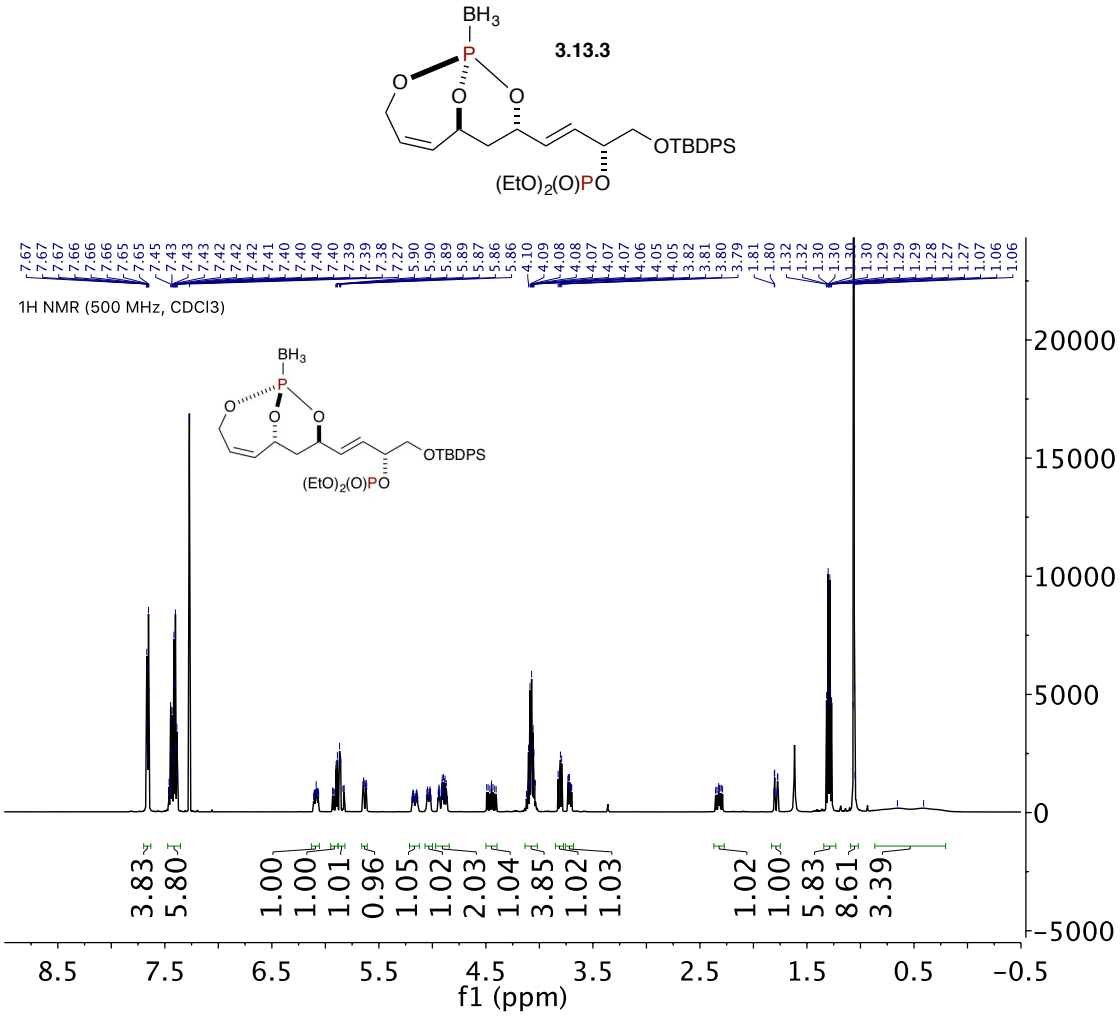

COSY (CDCl3)
f2 (ppm)
f1 (ppm)
BH3
OTBDPS
OH

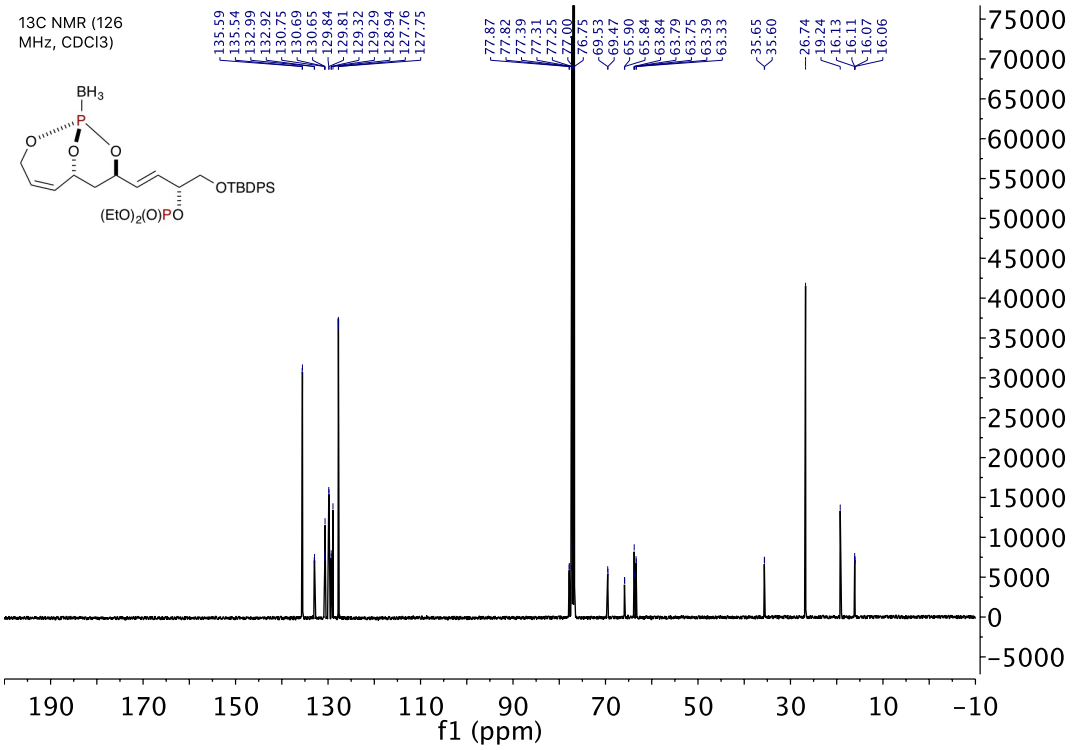

HSQC (CDCl3)
f2 (ppm)
f1 (ppm)
BH3
OTBDPS
OH

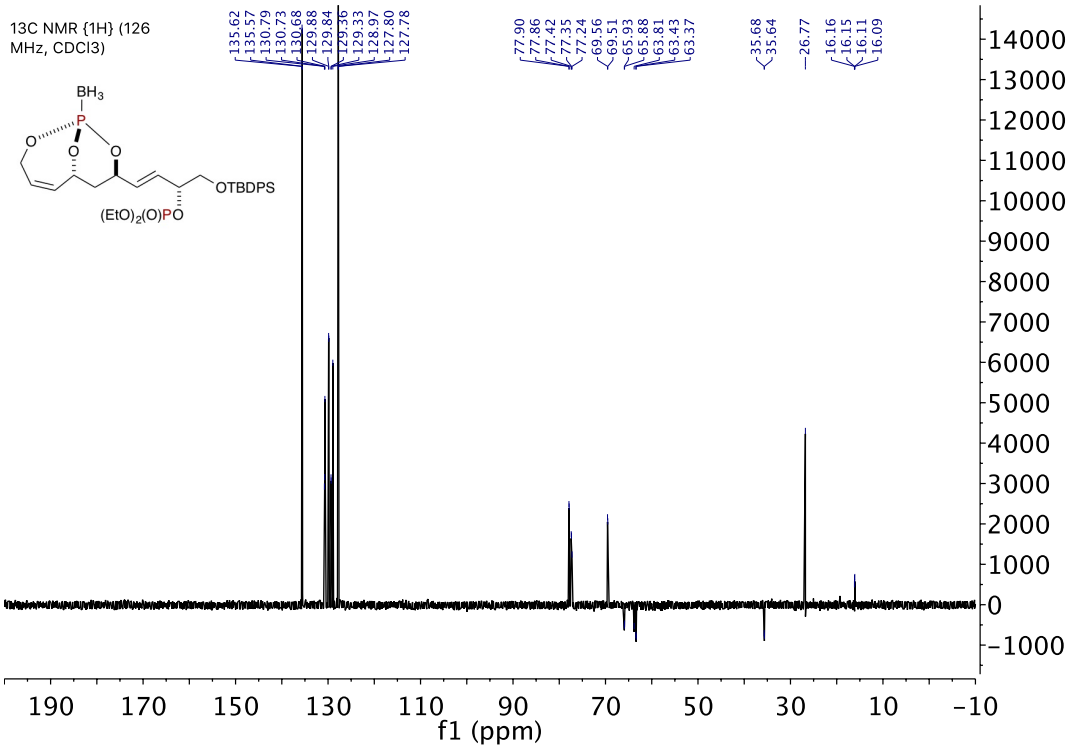

31P NMR (162 MHz, CDCl3)
113.41
112.50
BH3
P
O
O
O
OTBDPS
OH
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
120 90 60 30 0 -30 -60 -90 -120 -150 -180 -210 -240
f1 (ppm)

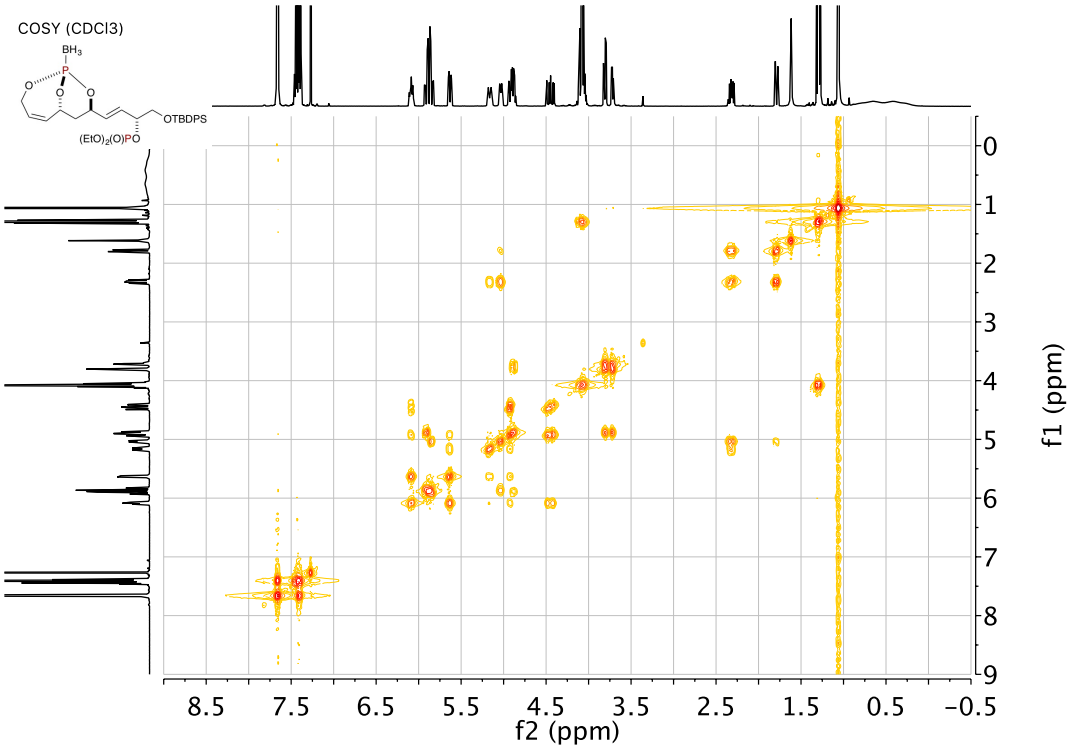

11B NMR (160 MHz, CDCl3)
-41.24
-42.00
-42.77
-43.54
-44.34
BH3
P
O
O
O
OTBDPS
OH
300000
280000
260000
240000
220000
200000
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
-20000
-25 -30 -35 -40 -45 -50 -55 -60 -65
f1 (ppm)

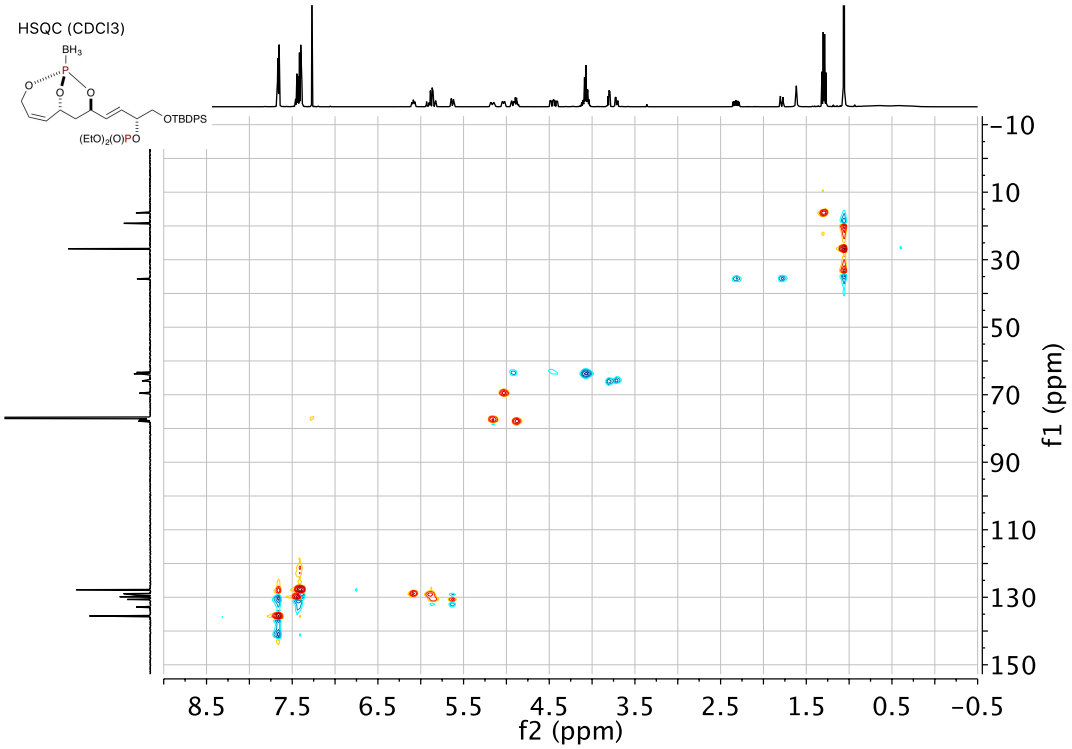
**(*R*,*E*)-4-((1*S*,6*R*,8*R*)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl-1-borane)-1-((*tert*-butyldiphenylsilyl)oxy)but-3-en-2-yl diethyl phosphate ($C_{30}H_{45}BO_8P_2Si$, 3.13.3)**

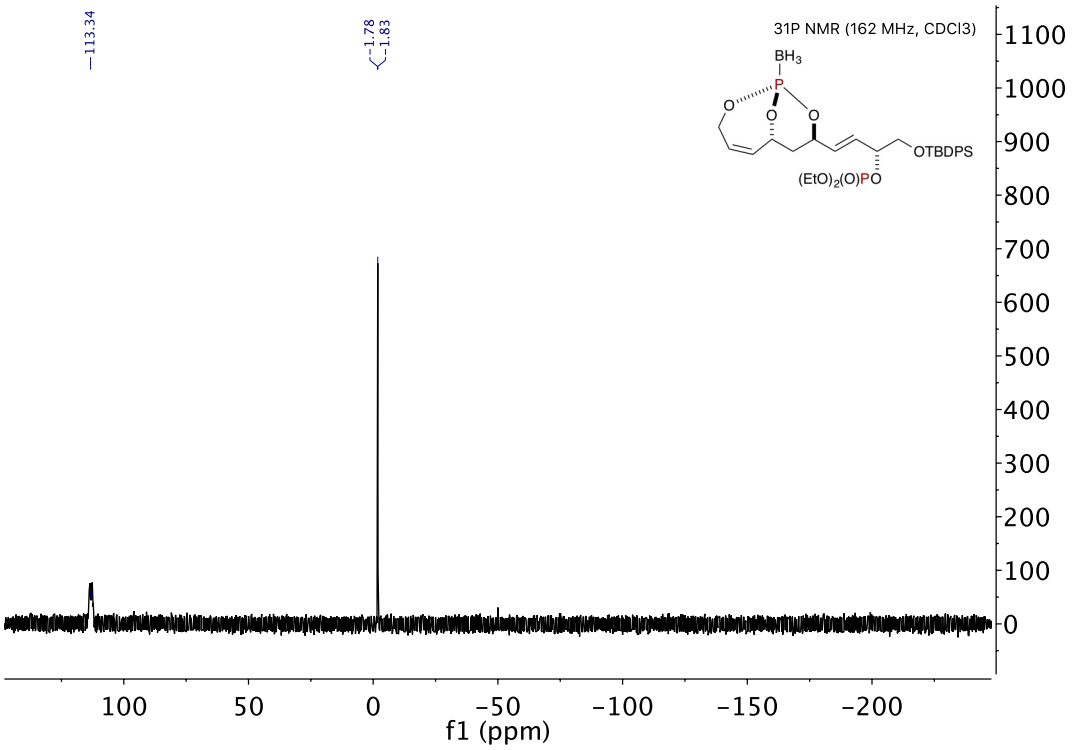


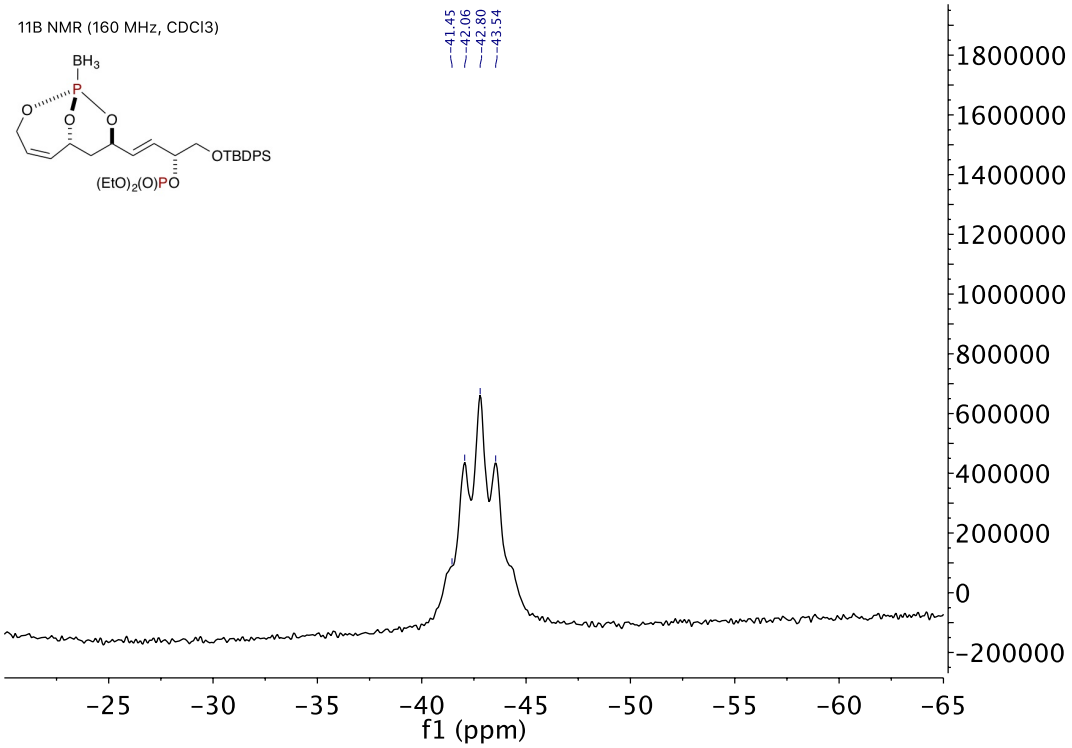

13C NMR (126 MHz, CDCl3)
135.59
135.54
132.99
132.92
130.75
130.69
130.65
129.84
129.81
129.32
129.29
128.94
127.76
127.75
77.87
77.82
77.39
77.31
77.25
77.00
76.75
69.53
69.47
65.90
65.84
63.84
63.79
63.75
63.39
63.33
35.65
35.60
26.74
19.24
16.13
16.11
16.07
16.06
BH3
P
O
O
O
OTBDPS
(EtO)2(O)PO
75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)


13C NMR {1H} (126 MHz, CDCl3)
135.62
135.57
130.79
130.73
130.68
129.88
129.84
129.36
129.33
128.97
127.80
127.78
77.90
77.86
77.42
77.35
77.24
69.56
69.51
65.93
65.88
63.81
63.43
63.37
35.68
35.64
26.77
16.16
16.15
16.11
16.09
BH3
P
O
O
O
OTBDPS
(EtO)2(O)PO
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

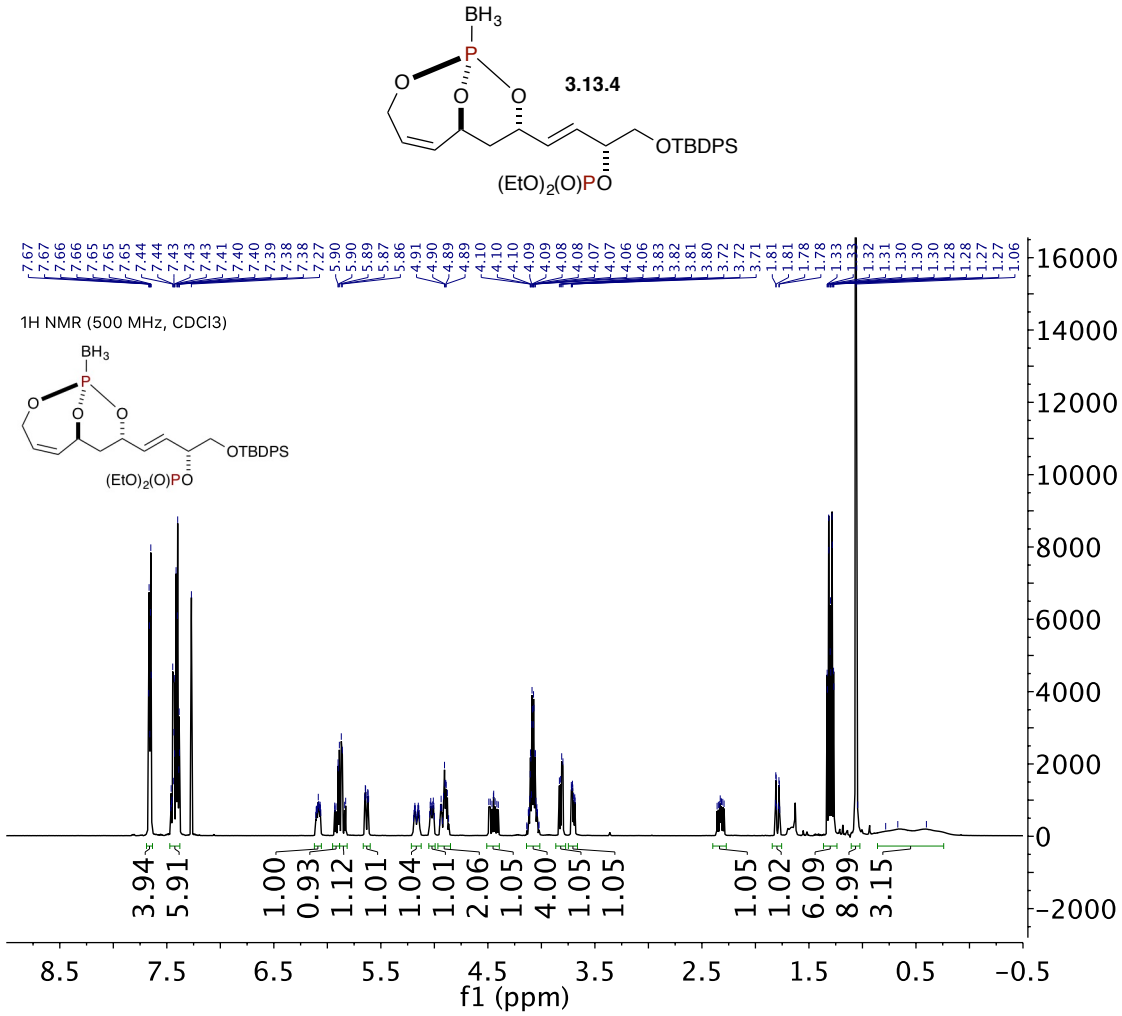

COSY (CDCl3)
BH3
OTBDPS
(EtO)2(O)PO
f1 (ppm)
f2 (ppm)
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
0
1
2
3
4
5
6
7
8
9

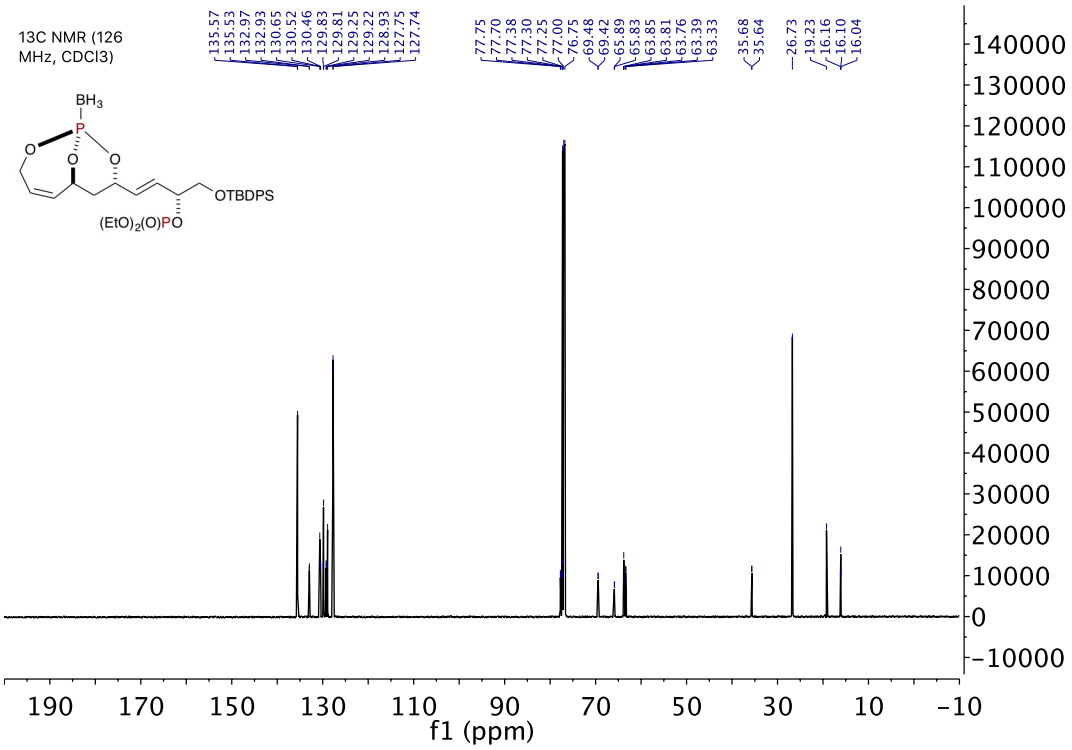

HSQC (CDCl3)
BH3
OTBDPS
(EtO)2(O)PO
f1 (ppm)
f2 (ppm)
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
-10
10
30
50
70
90
110
130
150

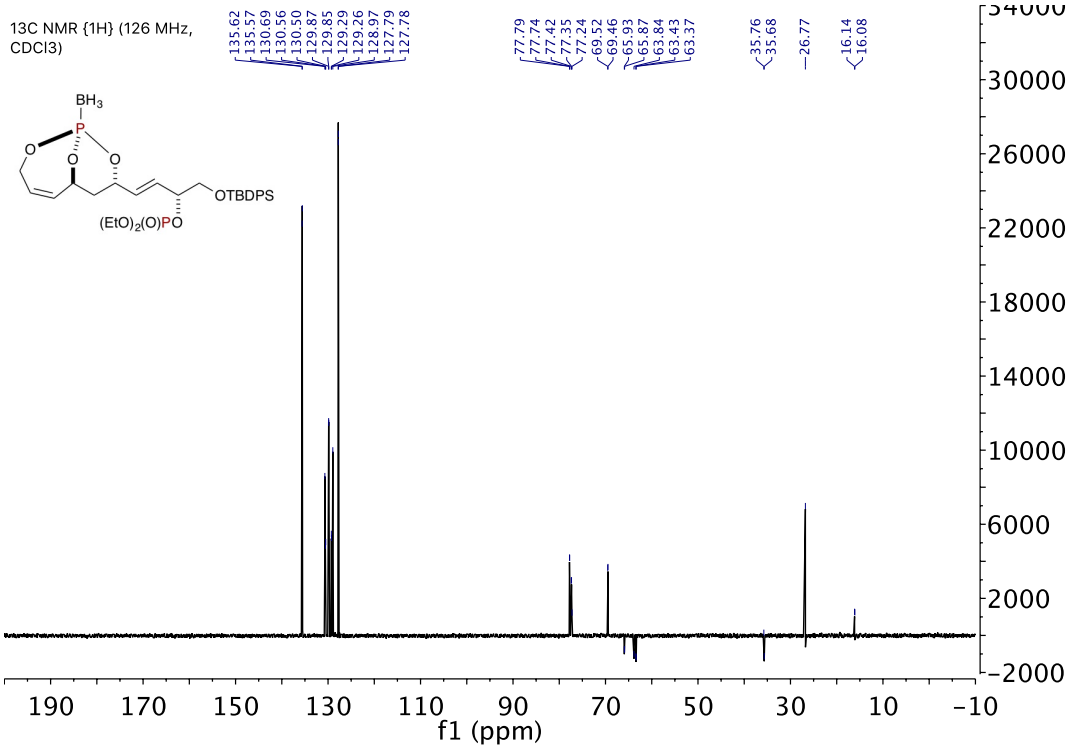

31P NMR (162 MHz, CDCl3)
113.34
1.78
1.83
BH3
P
O
O
O
OTBDPS
(EtO)2(O)PO
1100
1000
900
800
700
600
500
400
300
200
100
0
100
50
0
-50
-100
-150
-200
f1 (ppm)

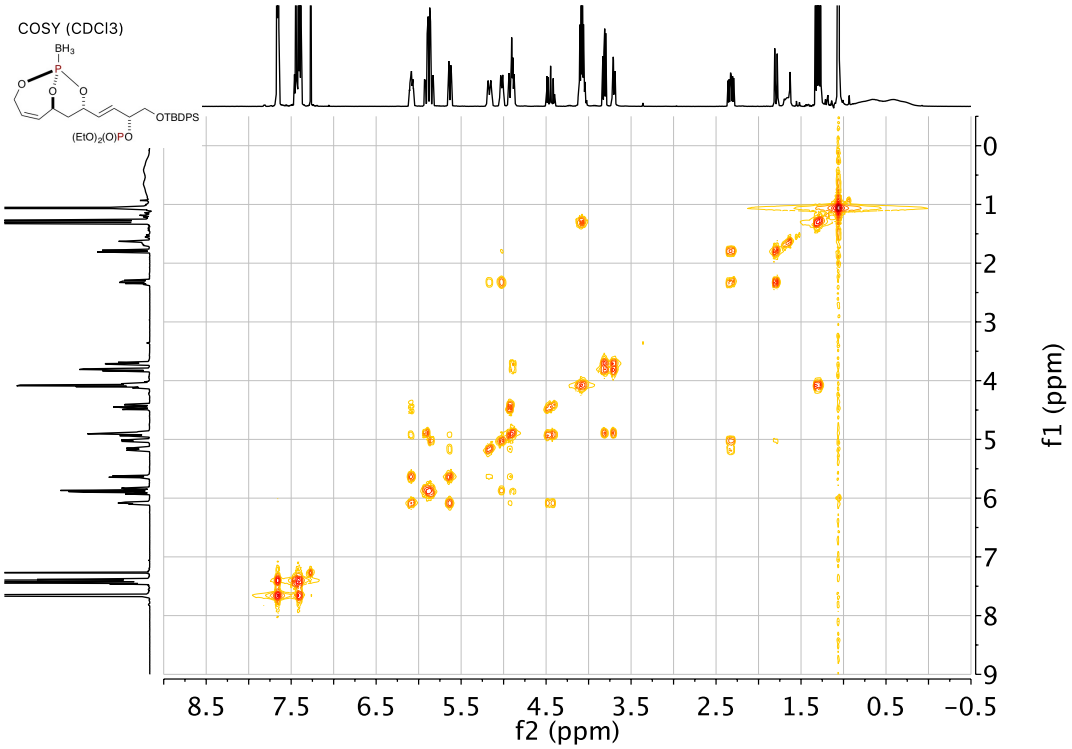

11B NMR (160 MHz, CDCl3)
41.45
42.06
42.80
43.54
BH3
P
O
O
O
OTBDPS
(EtO)2(O)PO
1800000
1600000
1400000
1200000
1000000
800000
600000
400000
200000
0
-200000
-25
-30
-35
-40
-45
-50
-55
-60
-65
f1 (ppm)

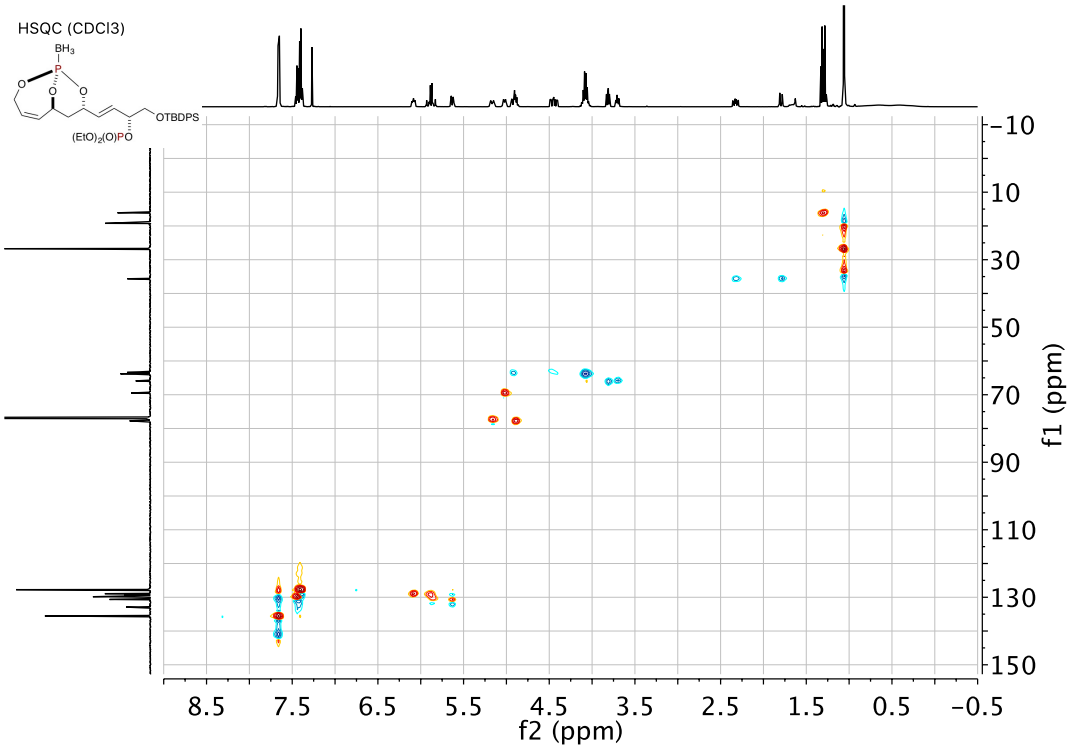
**(*R*,*E*)-4-((1*R*,6*S*,8*S*)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl-1-borane)-1-((*tert*-butyldiphenylsilyl)oxy)but-3-en-2-yl diethyl phosphate ($C_{30}H_{45}BO_8P_2Si$, 3.13.4)**

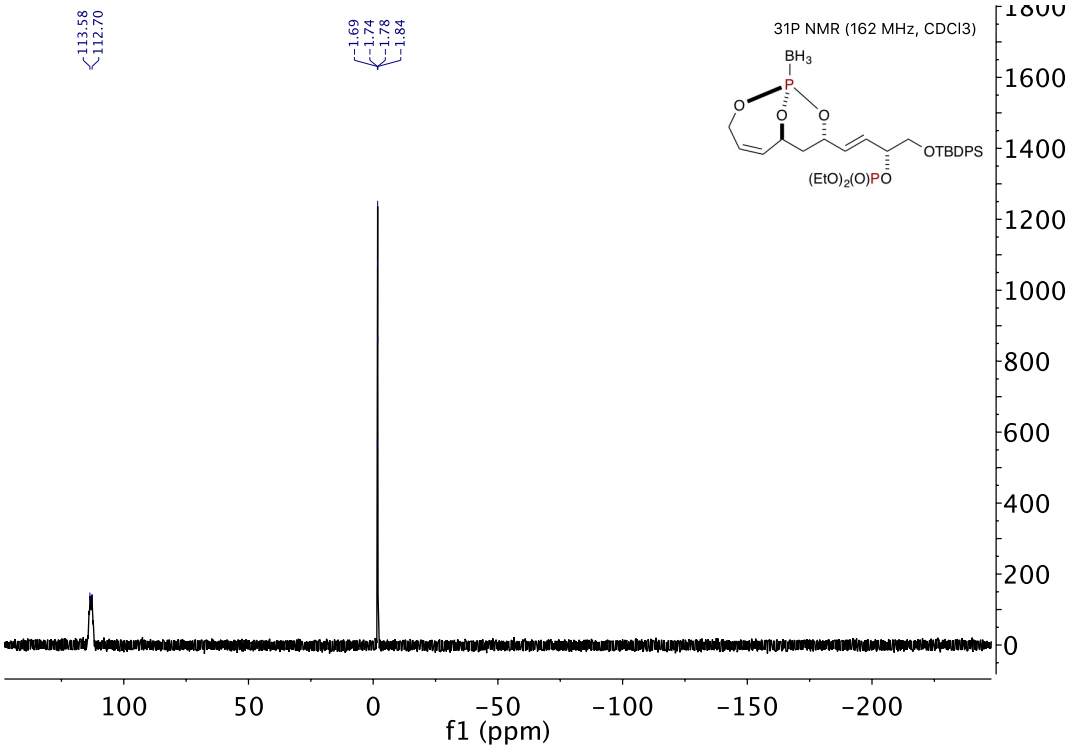


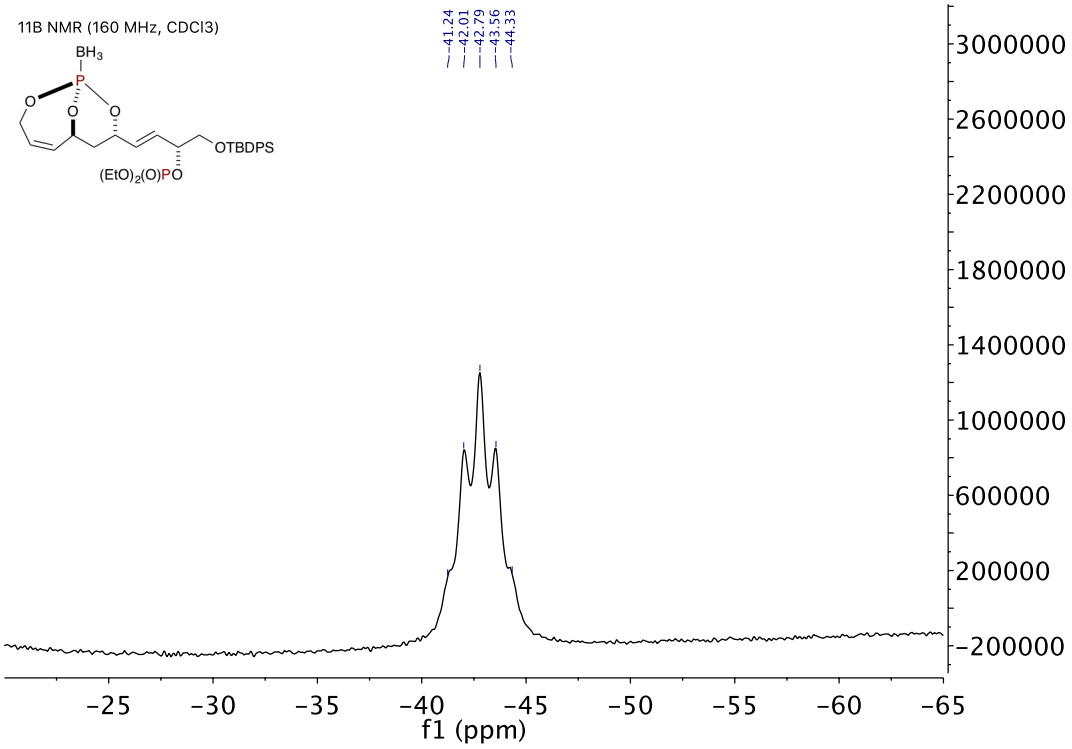

13C NMR (126 MHz, CDCl3)
BH3
P
O
O
O
OTBDPS
(EtO)2(O)PO
135.57
135.53
132.97
132.93
130.65
130.52
130.46
129.83
129.81
129.25
129.22
128.93
127.75
127.74
77.75
77.70
77.38
77.30
77.25
77.00
76.75
69.48
69.42
65.89
65.83
63.85
63.81
63.76
63.39
63.33
35.68
35.64
26.73
19.23
16.16
16.10
16.04
140000
130000
120000
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)


13C NMR {1H} (126 MHz, CDCl3)
BH3
P
O
O
O
OTBDPS
(EtO)2(O)PO
135.62
135.57
130.69
130.56
130.50
129.87
129.85
129.29
129.26
128.97
127.79
127.78
77.79
77.74
77.42
77.35
77.24
69.52
69.46
65.93
65.87
63.84
63.43
63.37
35.76
35.68
26.77
16.14
16.08
30000
26000
22000
18000
14000
10000
6000
2000
-2000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

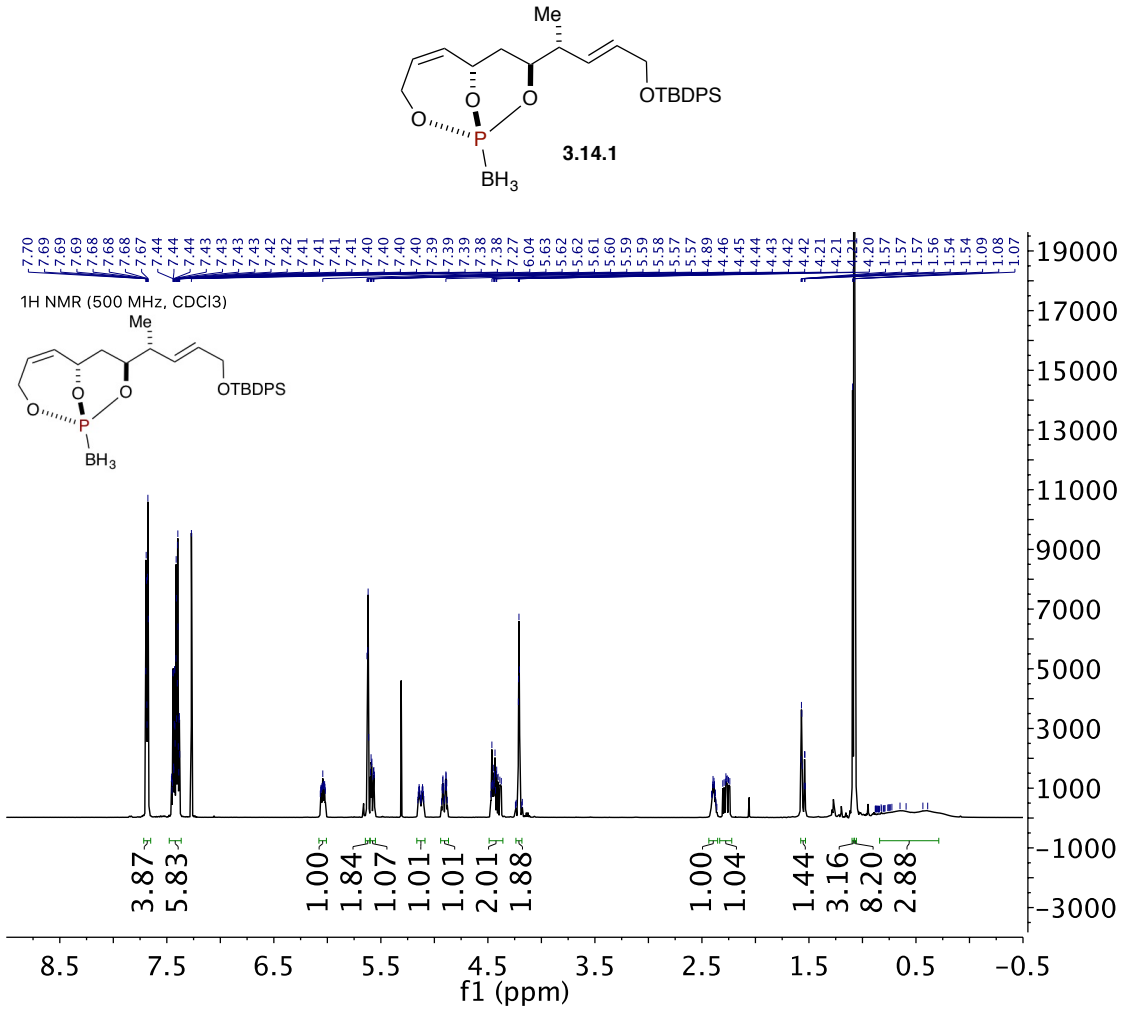

COSY (CDCl3)
BH3
OTBDPS
(EtO)2(O)PO
f1 (ppm)
f2 (ppm)
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
0
1
2
3
4
5
6
7
8
9

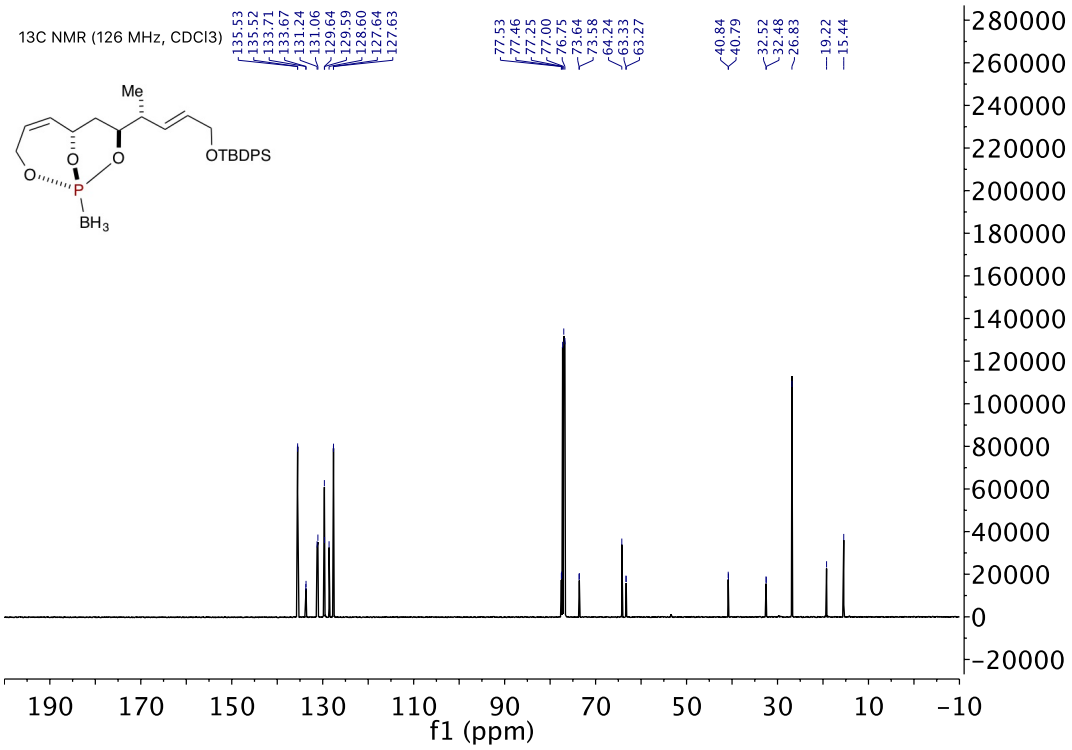

HSQC (CDCl3)
BH3
OTBDPS
(EtO)2(O)PO
f1 (ppm)
f2 (ppm)
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
-10
10
30
50
70
90
110
130
150

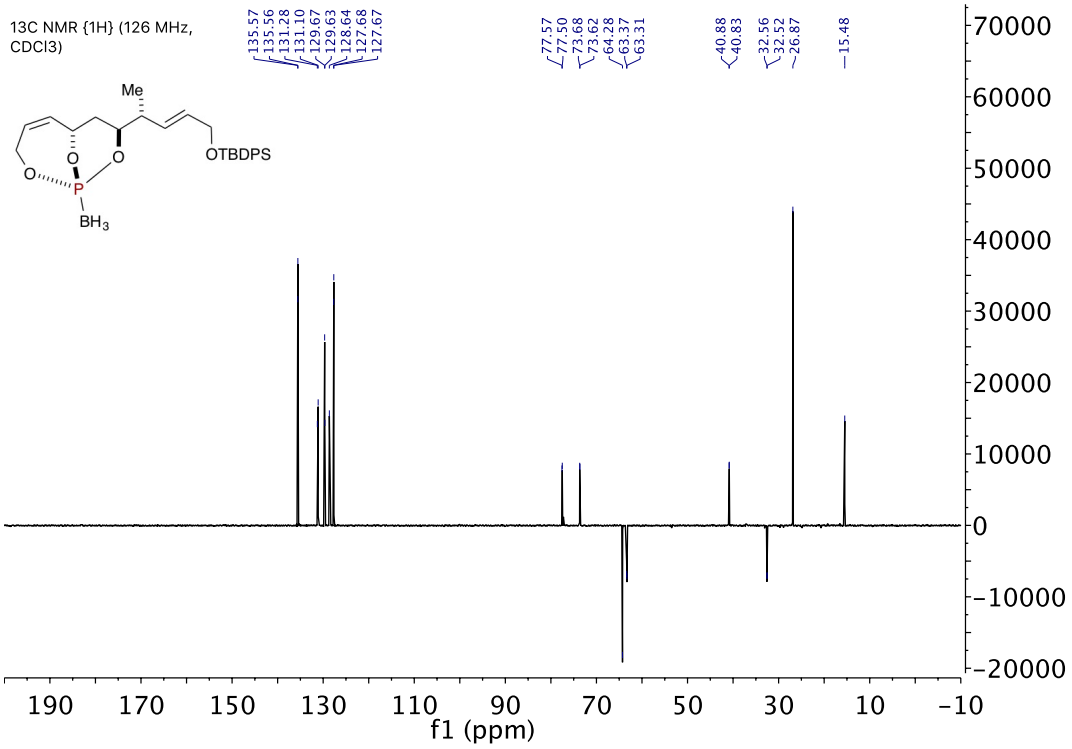

31P NMR (162 MHz, CDCl3)
BH3
P
O
O
O
OTBDPS
(EtO)2(O)PO
113.58
112.70
1.69
1.74
1.78
1.84
1600
1400
1200
1000
800
600
400
200
0
100
50
0
-50
-100
-150
-200
f1 (ppm)

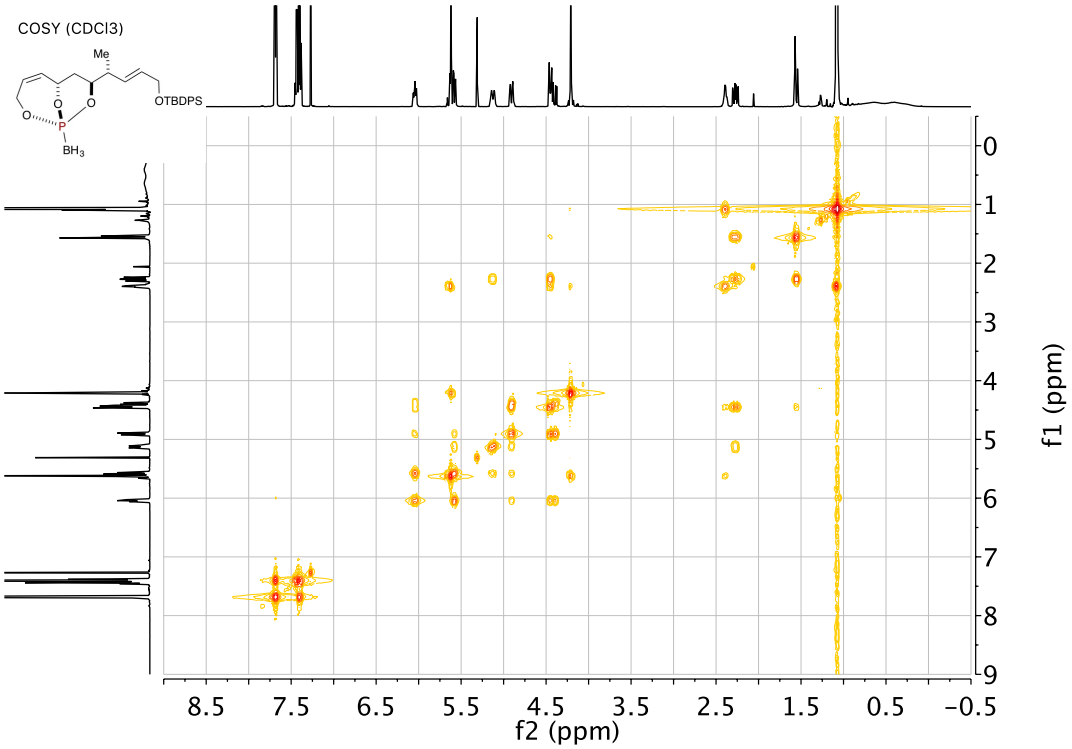

11B NMR (160 MHz, CDCl3)
BH3
P
O
O
O
OTBDPS
(EtO)2(O)PO
41.24
42.01
42.79
43.56
44.33
3000000
2600000
2200000
1800000
1400000
1000000
600000
200000
-200000
-25
-30
-35
-40
-45
-50
-55
-60
-65
f1 (ppm)

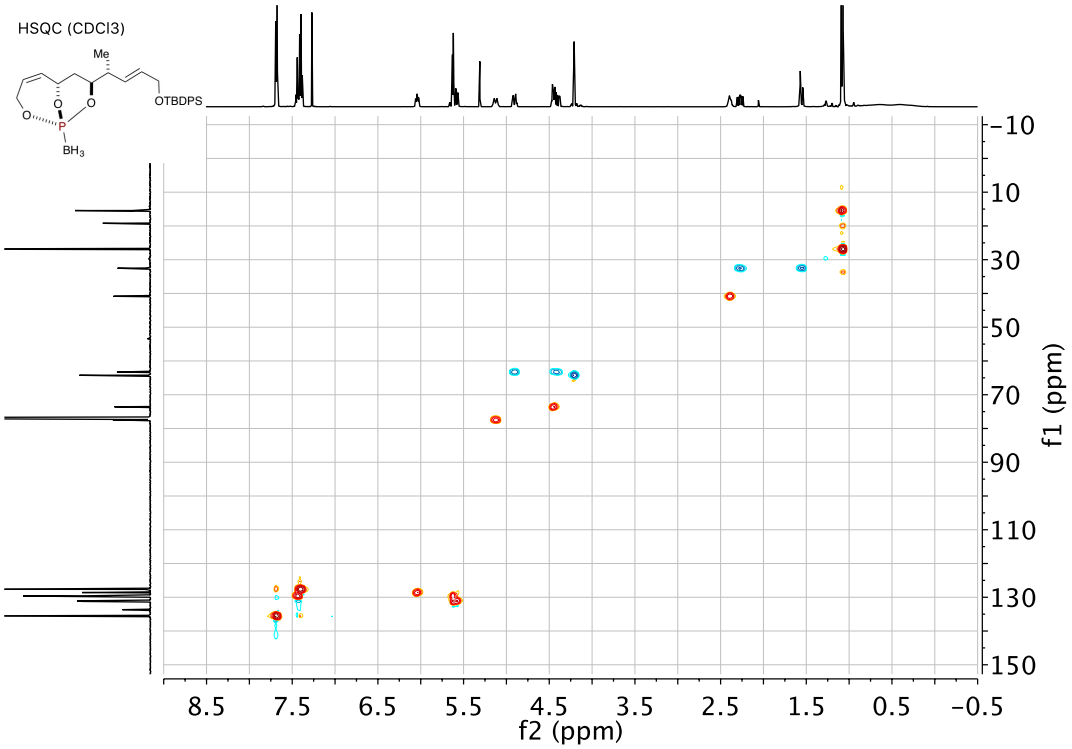
**(1*R*,6*S*,8*S*)-8-((*R*,*E*)-5-((*tert*-butyldiphenylsilyl)oxy)pent-3-en-2-yl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-borane ($C_{27}H_{38}BO_4PSi$, 3.14.1)**

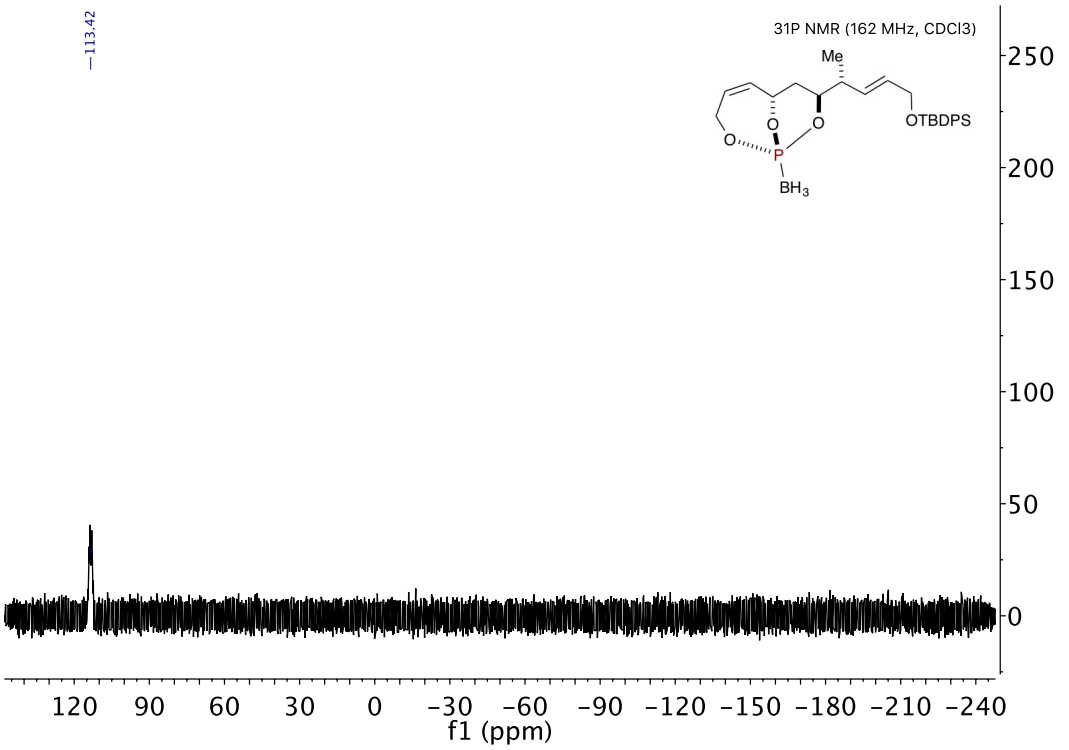


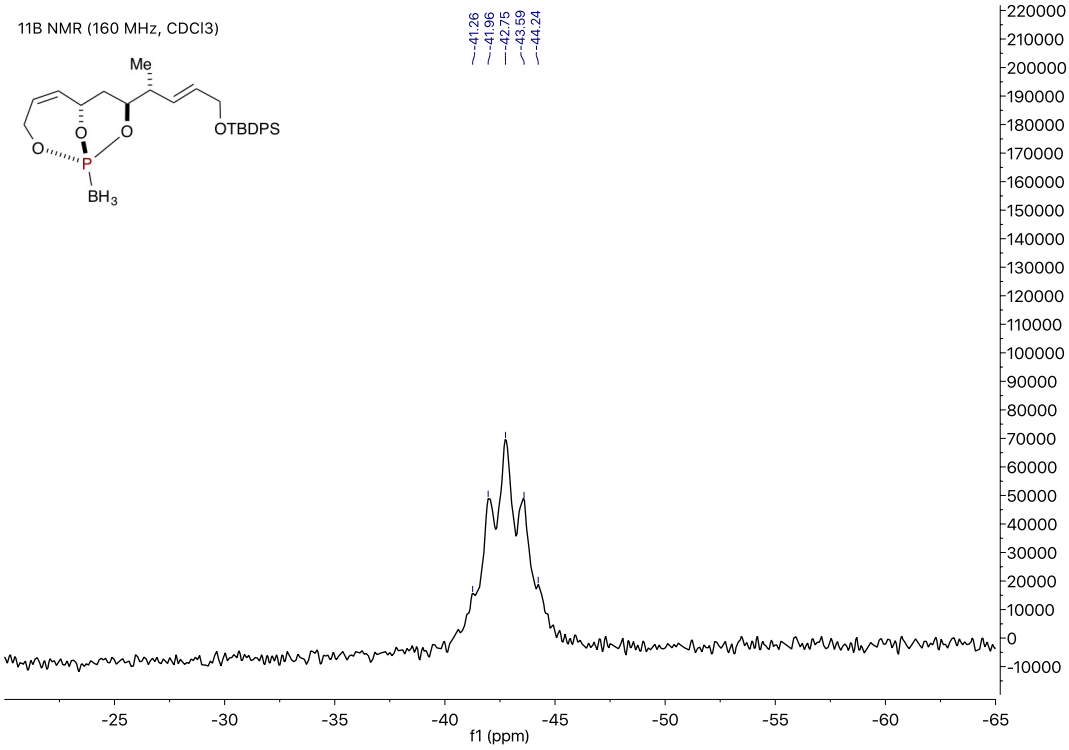

13C NMR (126 MHz, CDCl3)
135.53
135.52
133.71
133.67
131.24
131.06
129.64
129.59
128.60
127.64
127.63
77.53
77.46
77.25
77.00
76.75
73.64
73.58
64.24
63.33
63.27
40.84
40.79
32.52
32.48
26.83
19.22
15.44
Me
OTBDPS
O
O
O
P
BH3
280000
260000
240000
220000
200000
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
-20000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)


13C NMR {1H} (126 MHz, CDCl3)
135.57
135.56
131.28
131.10
129.67
129.63
128.64
127.68
127.67
77.57
77.50
73.68
73.62
64.28
63.37
63.31
40.88
40.83
32.56
32.52
26.87
15.48
Me
OTBDPS
O
O
O
P
BH3
70000
60000
50000
40000
30000
20000
10000
0
-10000
-20000
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

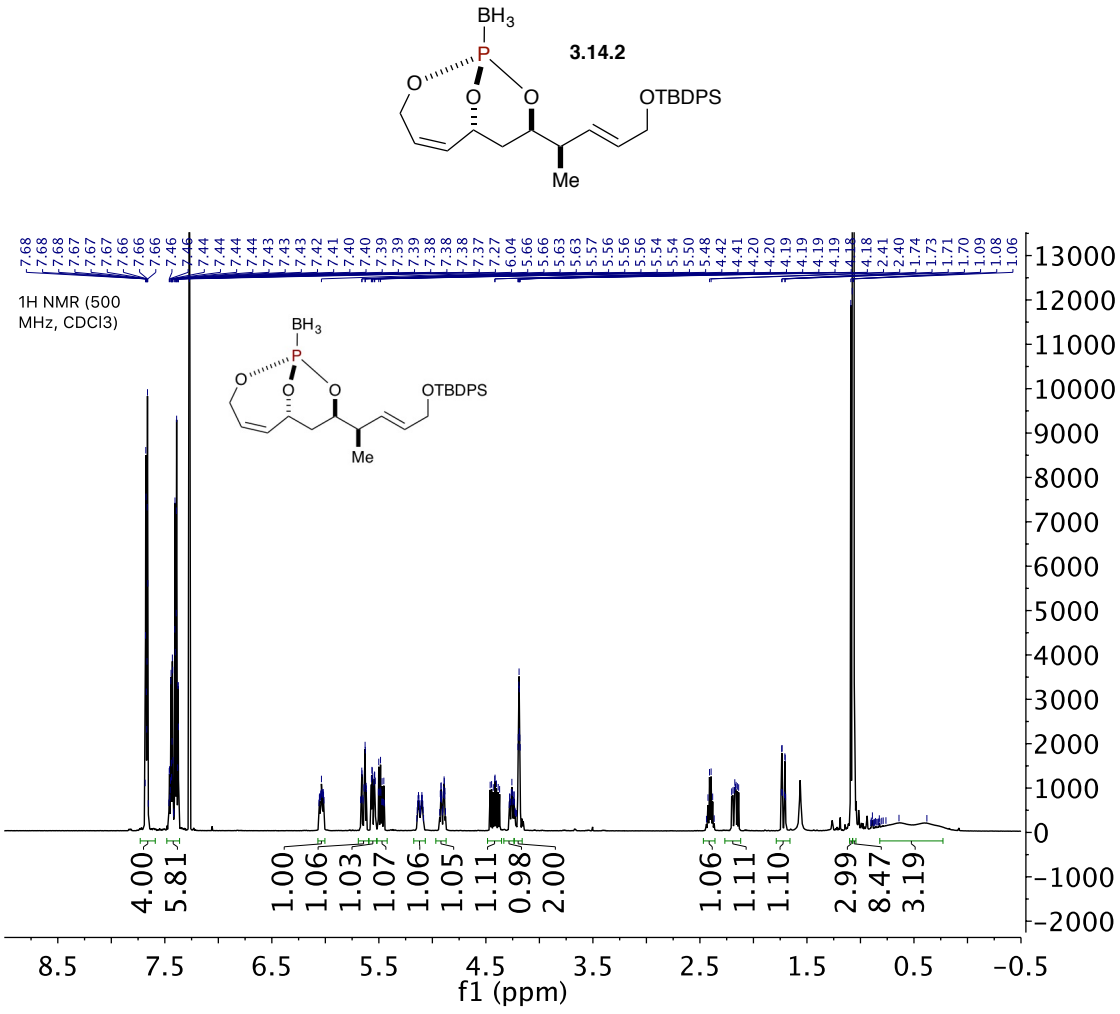

COSY (CDCl3)
Me
OTBDPS
O
O
O
P
BH3
0
1
2
3
4
5
6
7
8
9
f1 (ppm)
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f2 (ppm)

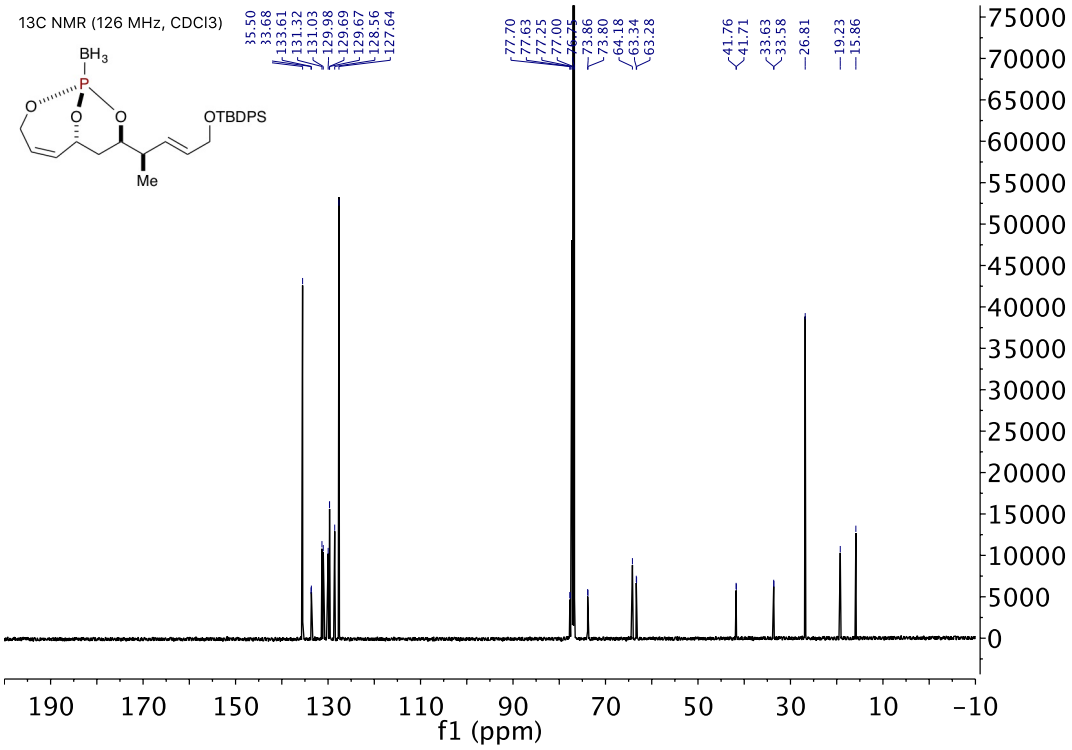

HSQC (CDCl3)
Me
OTBDPS
O
O
O
P
BH3
-10
10
30
50
70
90
110
130
150
f1 (ppm)
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f2 (ppm)

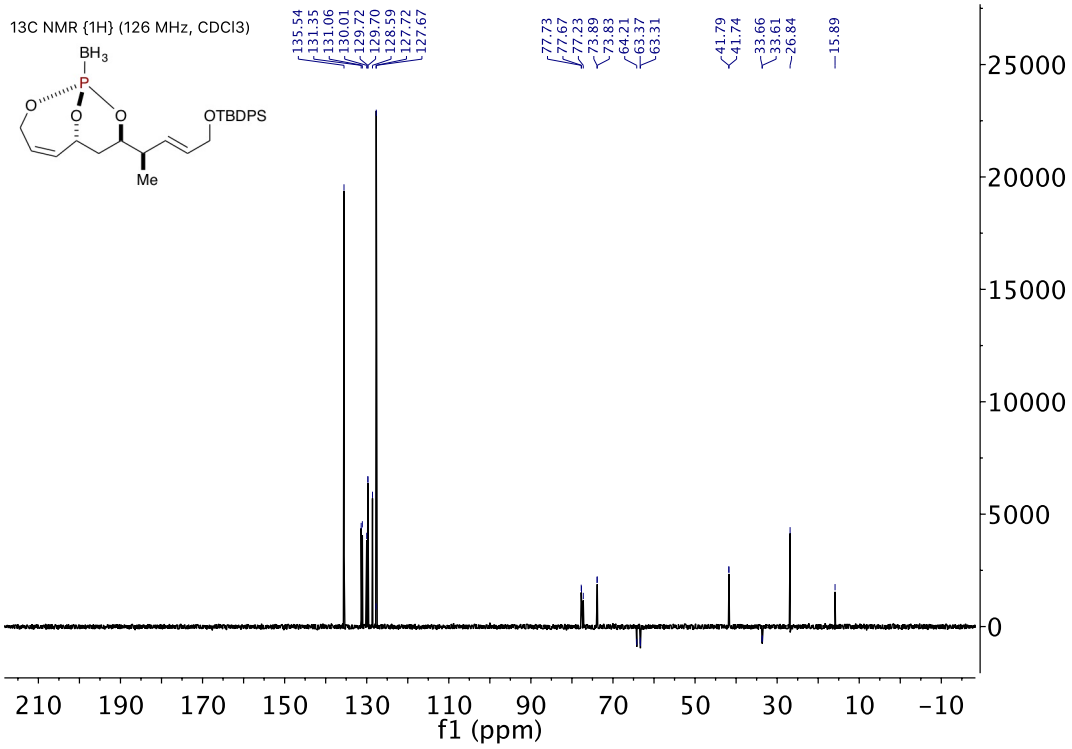

31P NMR (162 MHz, CDCl3)
113.42
Me
OTBDPS
O
O
O
P
BH3
250
200
150
100
50
0
120 90 60 30 0 -30 -60 -90 -120 -150 -180 -210 -240
f1 (ppm)

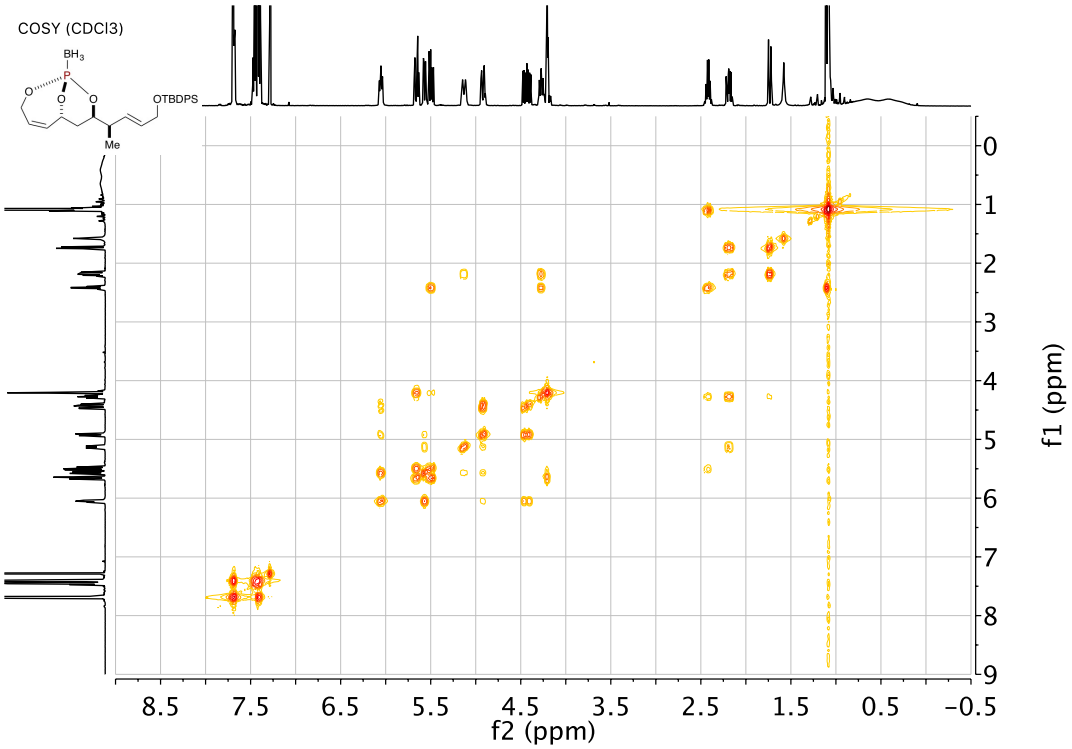

11B NMR (160 MHz, CDCl3)
41.26
41.96
42.75
43.59
44.24
Me
OTBDPS
O
O
O
P
BH3
220000
210000
200000
190000
180000
170000
160000
150000
140000
130000
120000
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
-25 -30 -35 -40 -45 -50 -55 -60 -65
f1 (ppm)

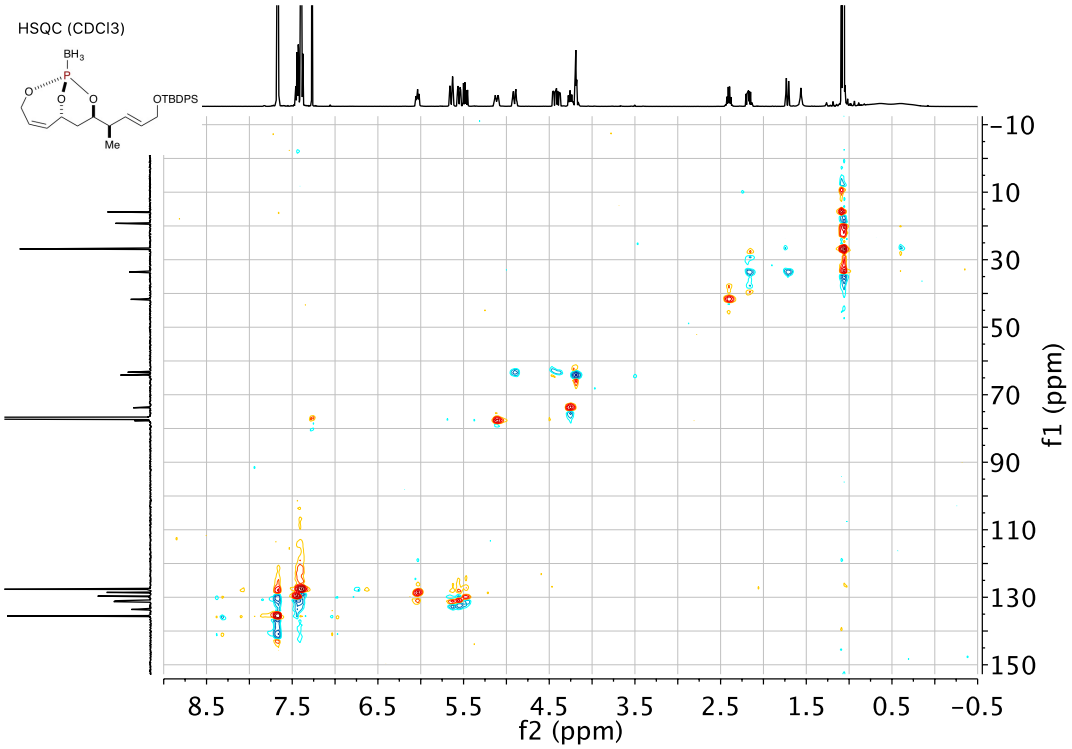
**(1*S*,6*R*,8*R*)-8-((*R*,*E*)-5-((*tert*-butyldiphenylsilyl)oxy)pent-3-en-2-yl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-borane ($C_{27}H_{38}BO_4PSi$, 3.14.2)**

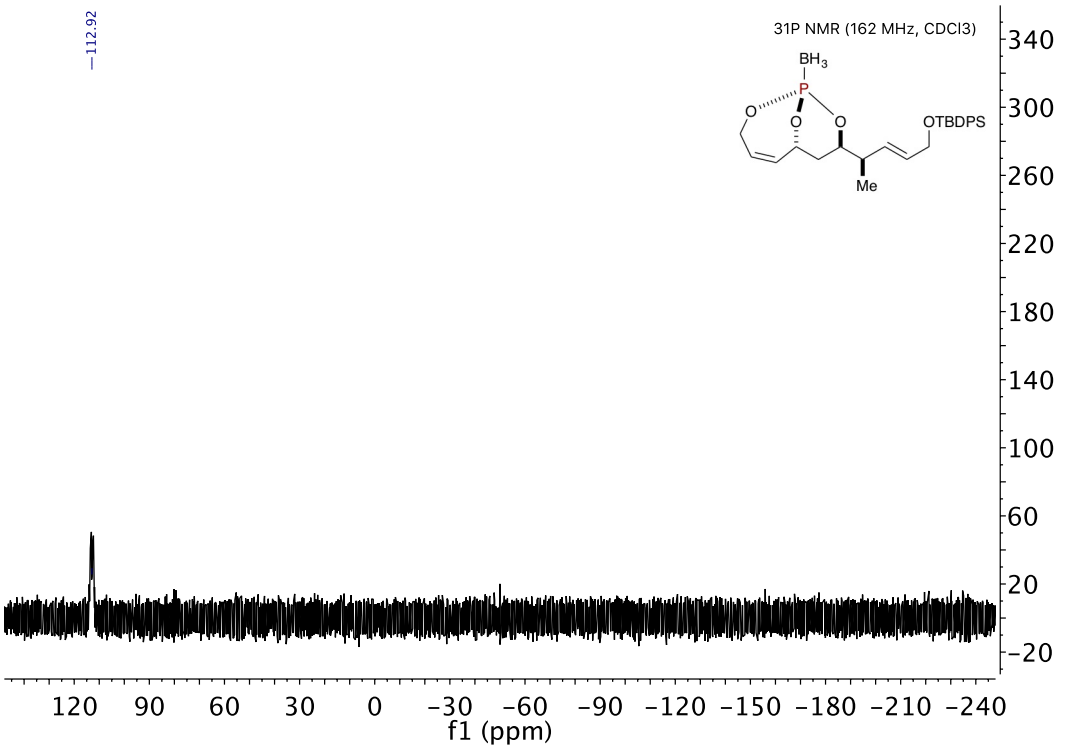


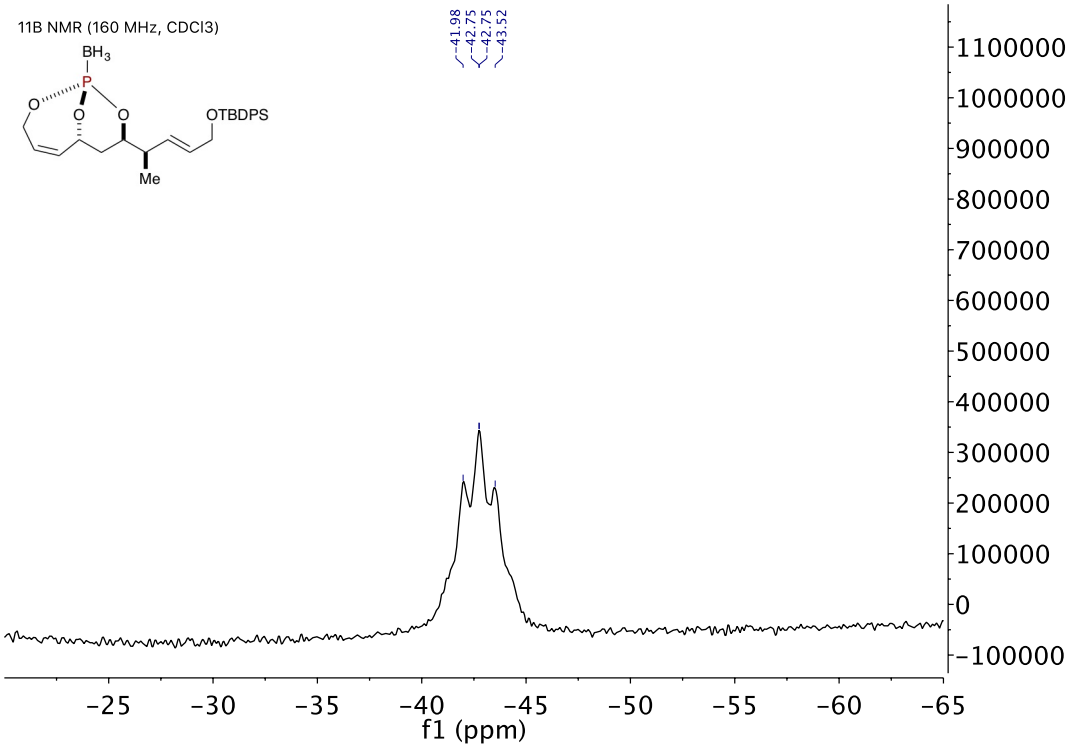

13C NMR (126 MHz, CDCl3)
BH3
P
O
O
O
OTBDPS
Me
135.50
133.68
133.61
131.32
131.03
129.98
129.69
129.67
128.56
127.64
77.70
77.63
77.25
77.00
76.75
73.86
73.80
64.18
63.34
63.28
41.76
41.71
33.63
33.58
26.81
19.23
15.86
75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)


13C NMR {1H} (126 MHz, CDCl3)
BH3
P
O
O
O
OTBDPS
Me
135.54
131.35
131.06
130.01
129.72
129.70
128.59
127.72
127.67
77.73
77.67
77.23
73.89
73.83
64.21
63.37
63.31
41.79
41.74
33.66
33.61
26.84
15.89
25000
20000
15000
10000
5000
0
210
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

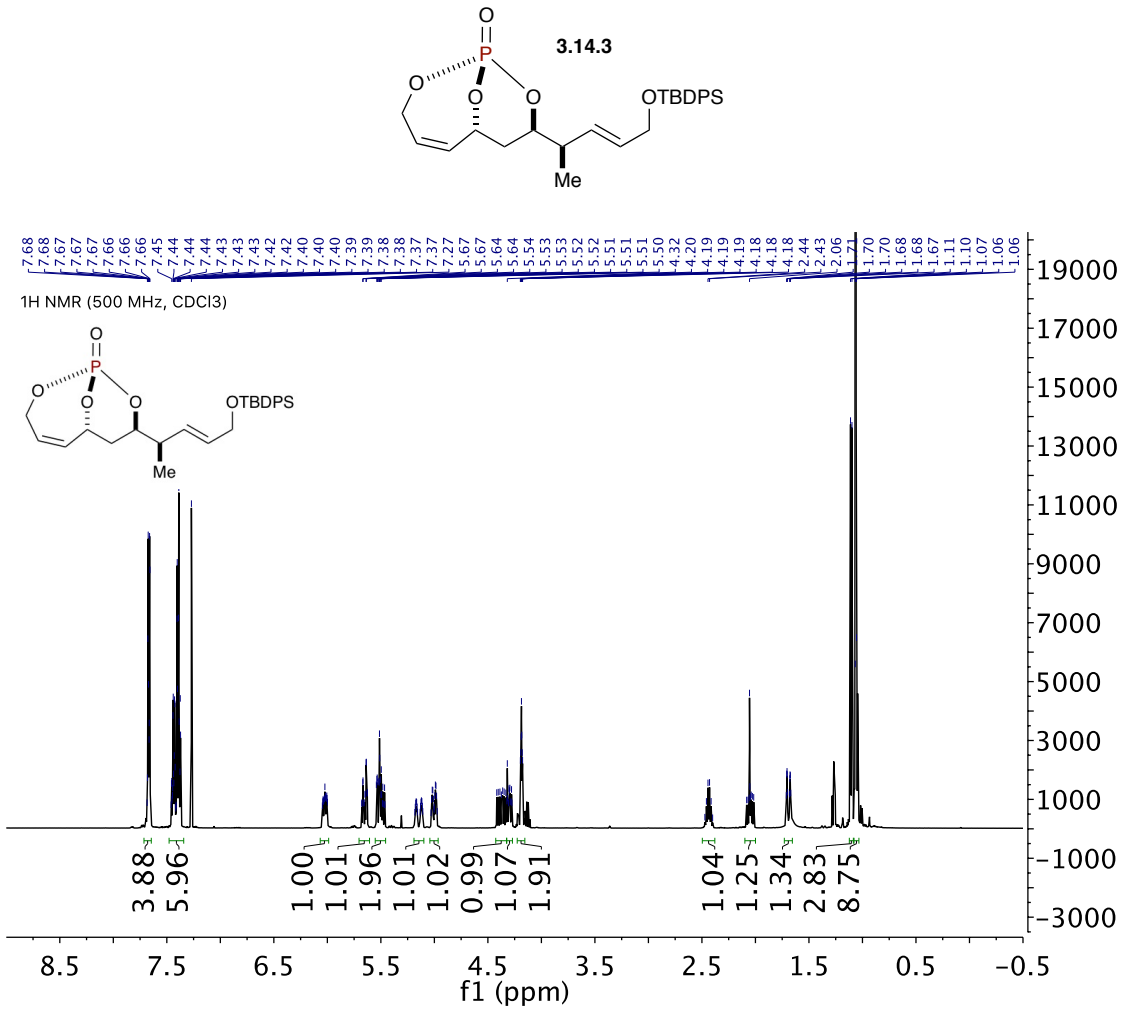

COSY (CDCl3)
BH3
P
O
O
O
OTBDPS
Me
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f2 (ppm)
0
1
2
3
4
5
6
7
8
9
f1 (ppm)

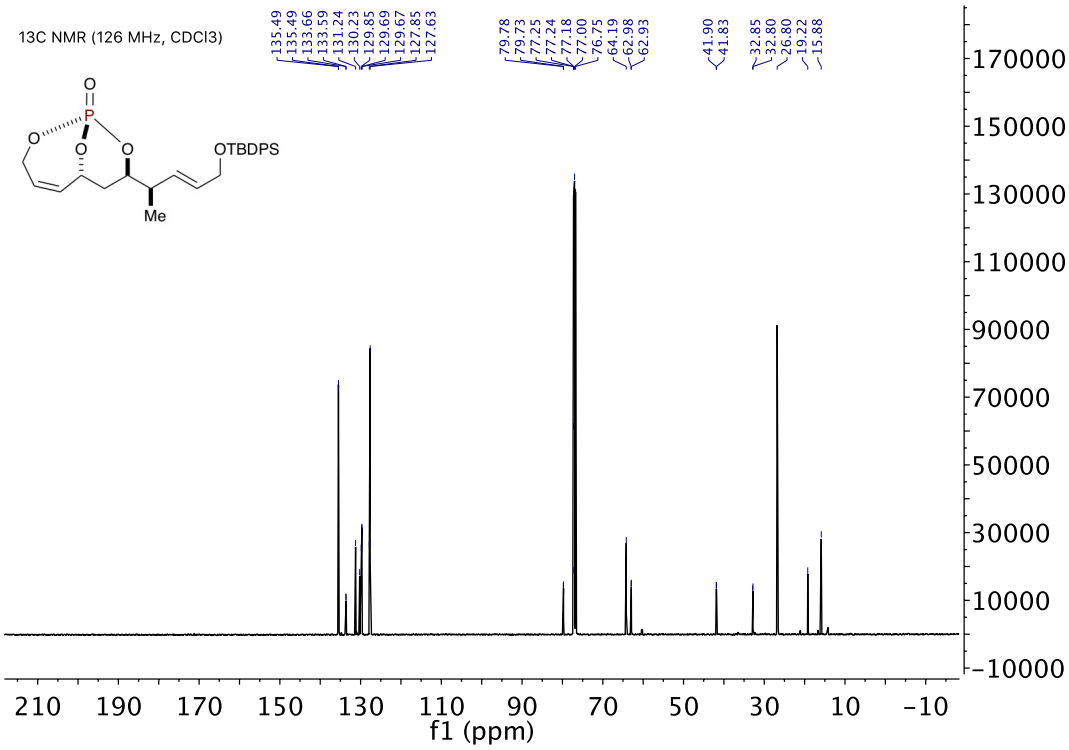

HSQC (CDCl3)
BH3
P
O
O
O
OTBDPS
Me
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f2 (ppm)
-10
10
30
50
70
90
110
130
150
f1 (ppm)

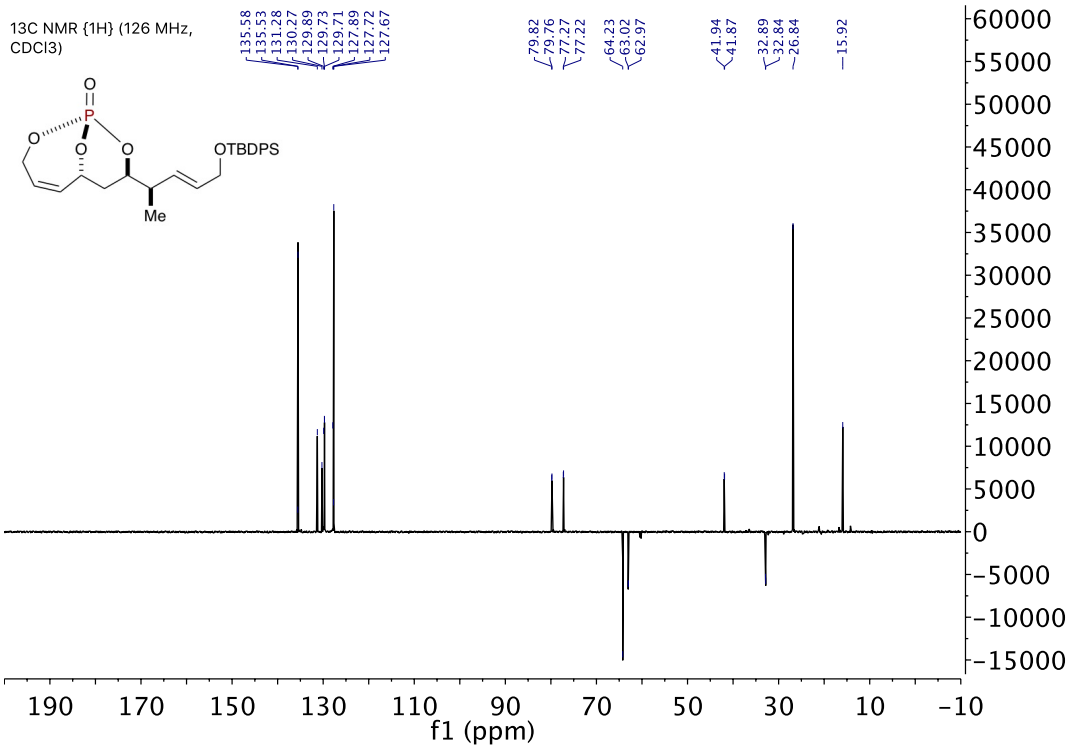

112.92
31P NMR (162 MHz, CDCl3)
BH3
P
O
O
O
OTBDPS
Me
340
300
260
220
180
140
100
60
20
-20
120 90 60 30 0 -30 -60 -90 -120 -150 -180 -210 -240
f1 (ppm)

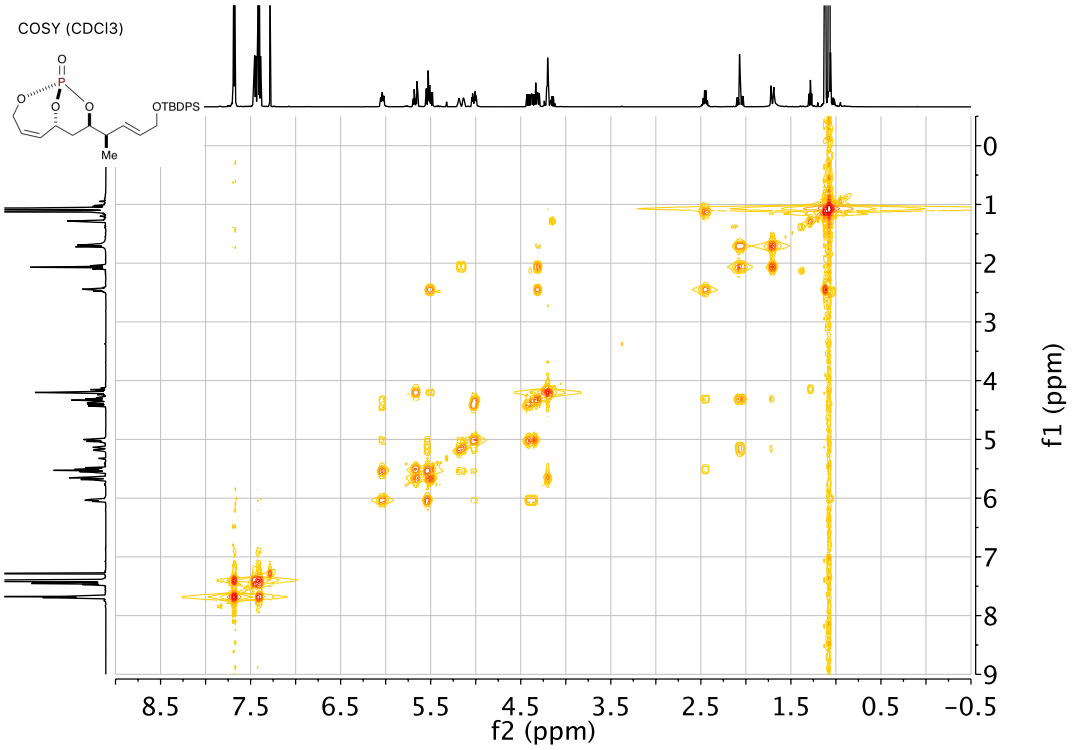

11B NMR (160 MHz, CDCl3)
BH3
P
O
O
O
OTBDPS
Me
41.98
42.75
42.75
43.52
1100000
1000000
900000
800000
700000
600000
500000
400000
300000
200000
100000
0
-100000
-25 -30 -35 -40 -45 -50 -55 -60 -65
f1 (ppm)

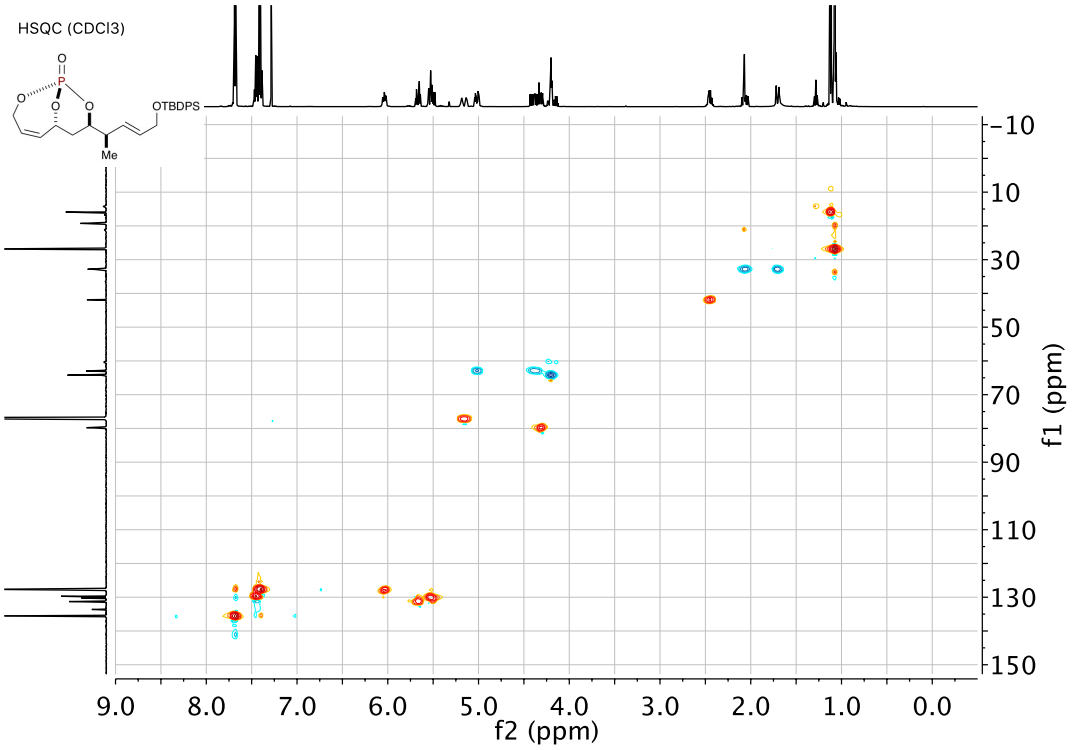
**(1*S*,6*R*,8*R*)-8-((*R*,*E*)-5-((*tert*-butyldiphenylsilyl)oxy)pent-3-en-2-yl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-oxide ($C_{27}H_{35}O_5PSi$, 3.14.3)**

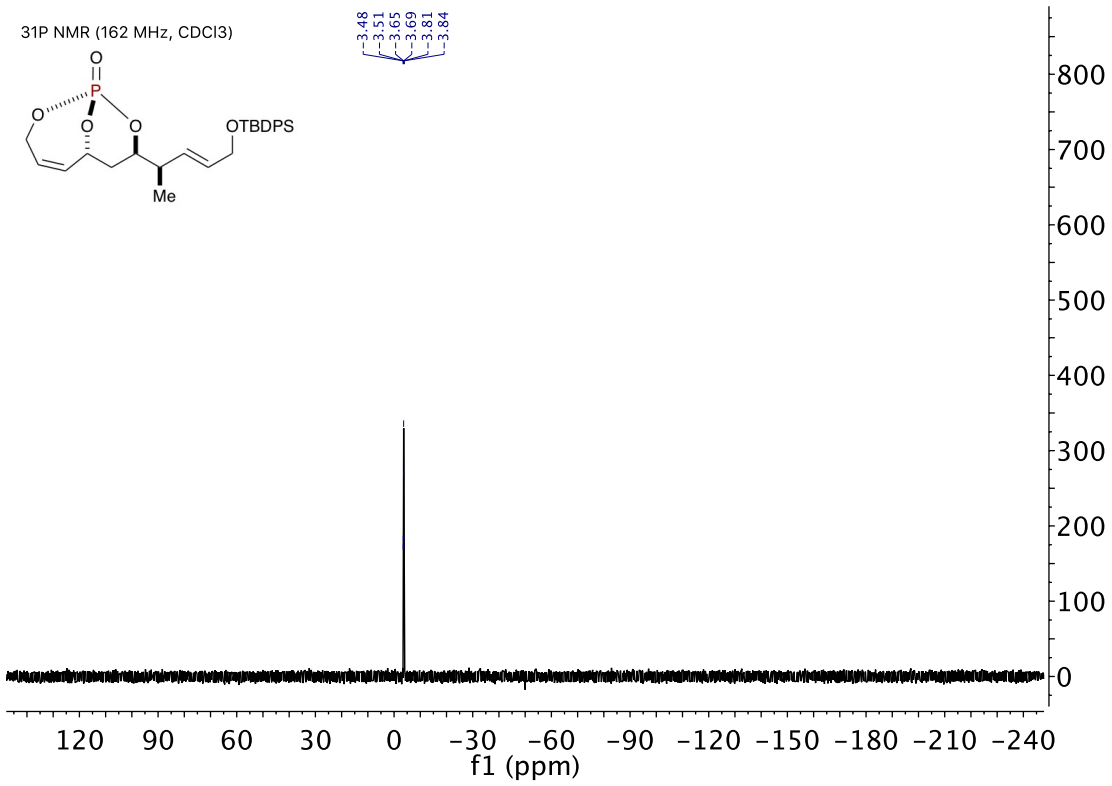



13C NMR (126 MHz, CDCl3)
135.49
135.49
133.66
133.59
131.24
130.23
129.85
129.69
129.67
127.85
127.63
79.78
79.73
77.25
77.24
77.18
77.00
76.75
64.19
62.98
62.93
41.90
41.83
32.85
32.80
26.80
19.22
15.88
OTBDPS
Me
f1 (ppm)

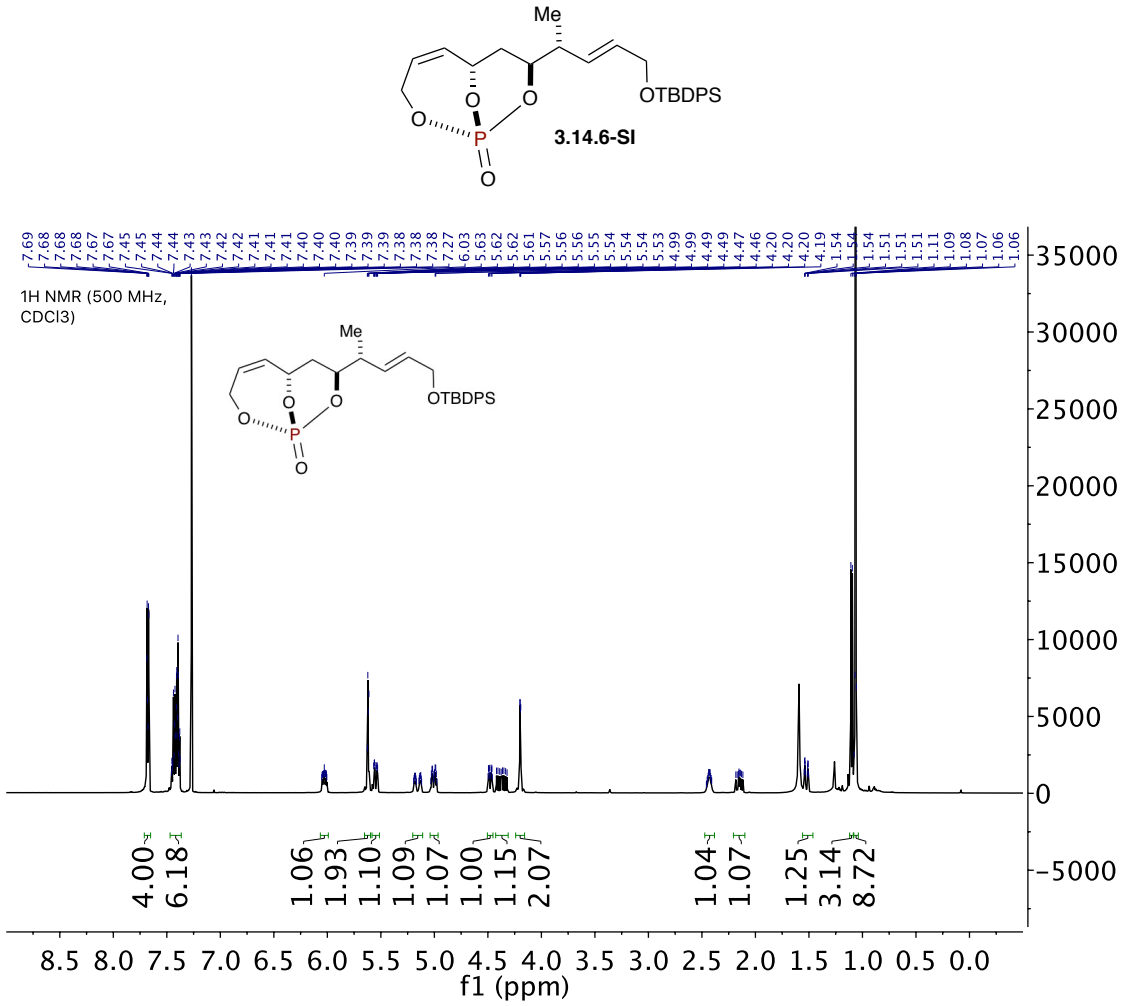

13C NMR {1H} (126 MHz, CDCl3)
135.58
135.53
131.28
130.27
129.89
129.73
129.71
127.89
127.72
127.67
79.82
79.76
77.27
77.22
64.23
63.02
62.97
41.94
41.87
32.89
32.84
26.84
15.92
OTBDPS
Me
f1 (ppm)

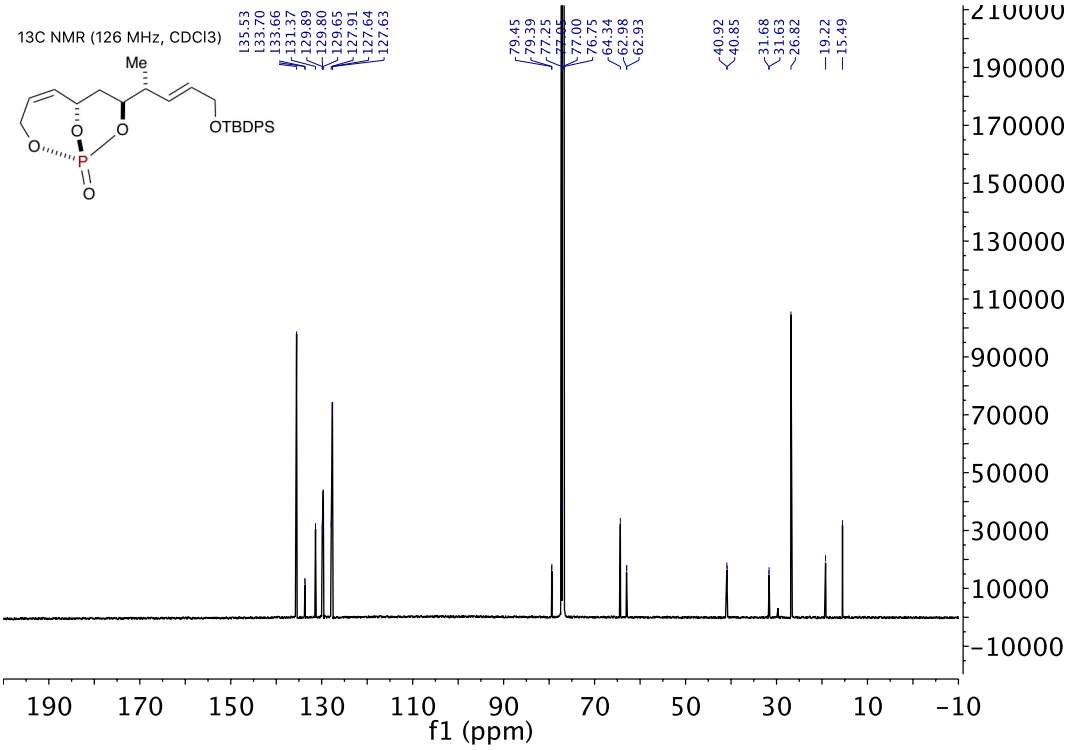

COSY (CDCl3)
OTBDPS
Me
f2 (ppm)
f1 (ppm)

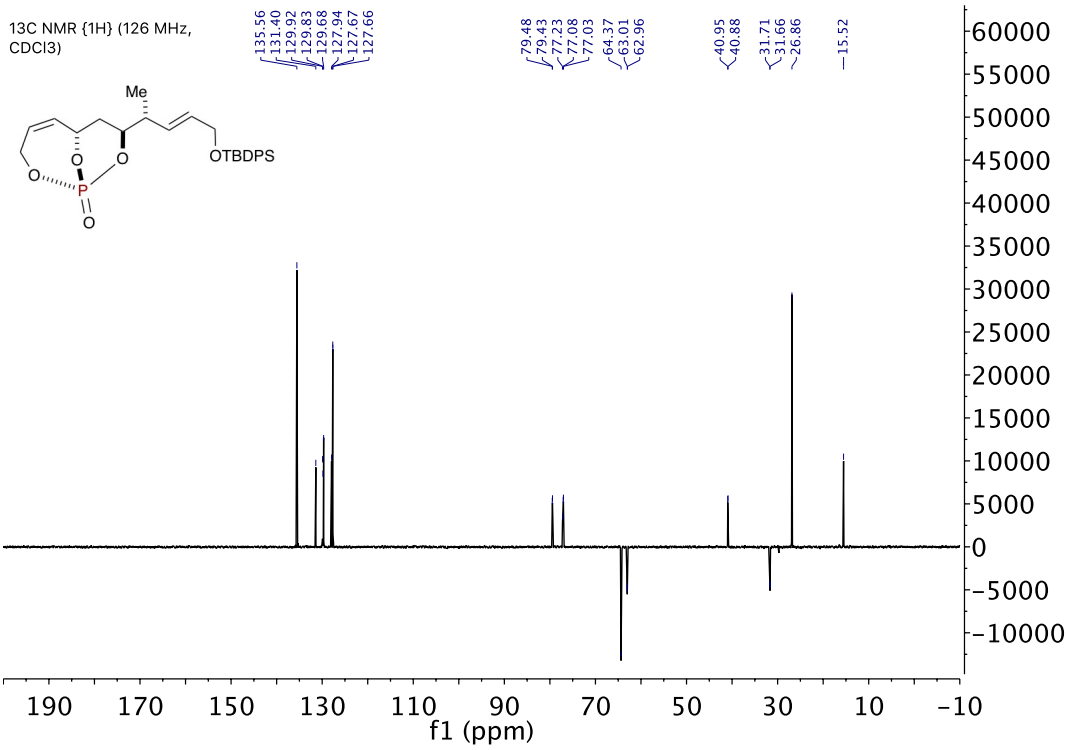

HSQC (CDCl3)
OTBDPS
Me
f2 (ppm)
f1 (ppm)

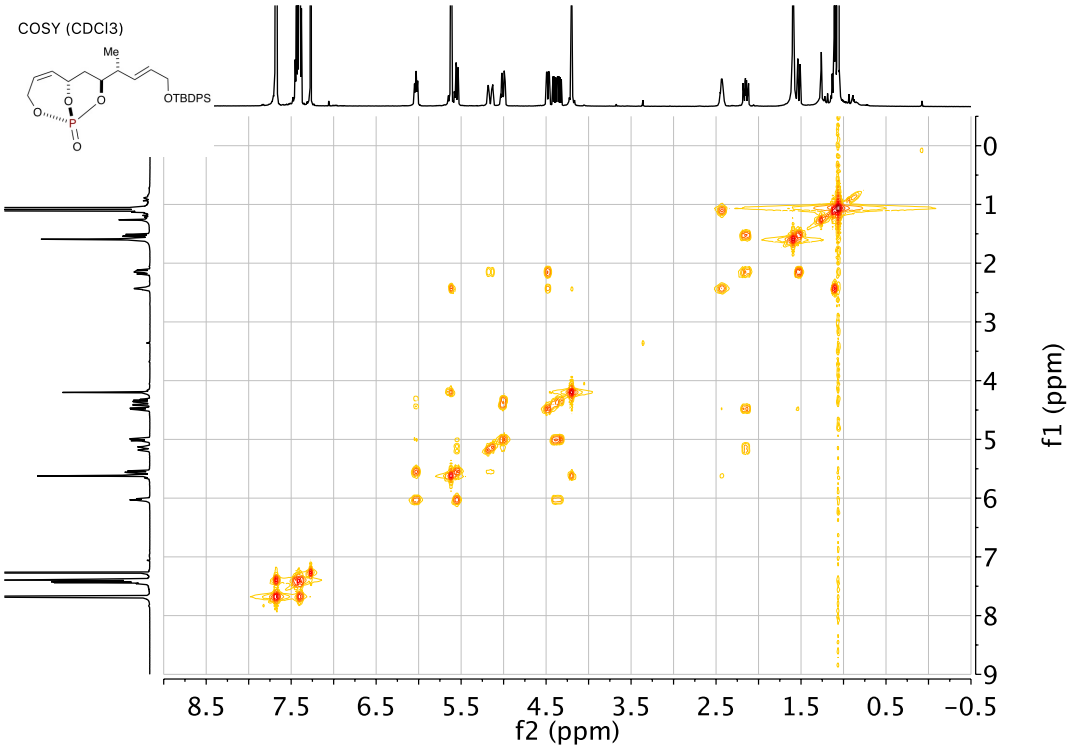

31P NMR (162 MHz, CDCl3)
3.48
3.51
3.65
3.69
3.81
3.84
O
P
O
O
O
OTBDPS
Me
800
700
600
500
400
300
200
100
0
120
90
60
30
0
-30
-60
-90
-120
-150
-180
-210
-240
f1 (ppm)

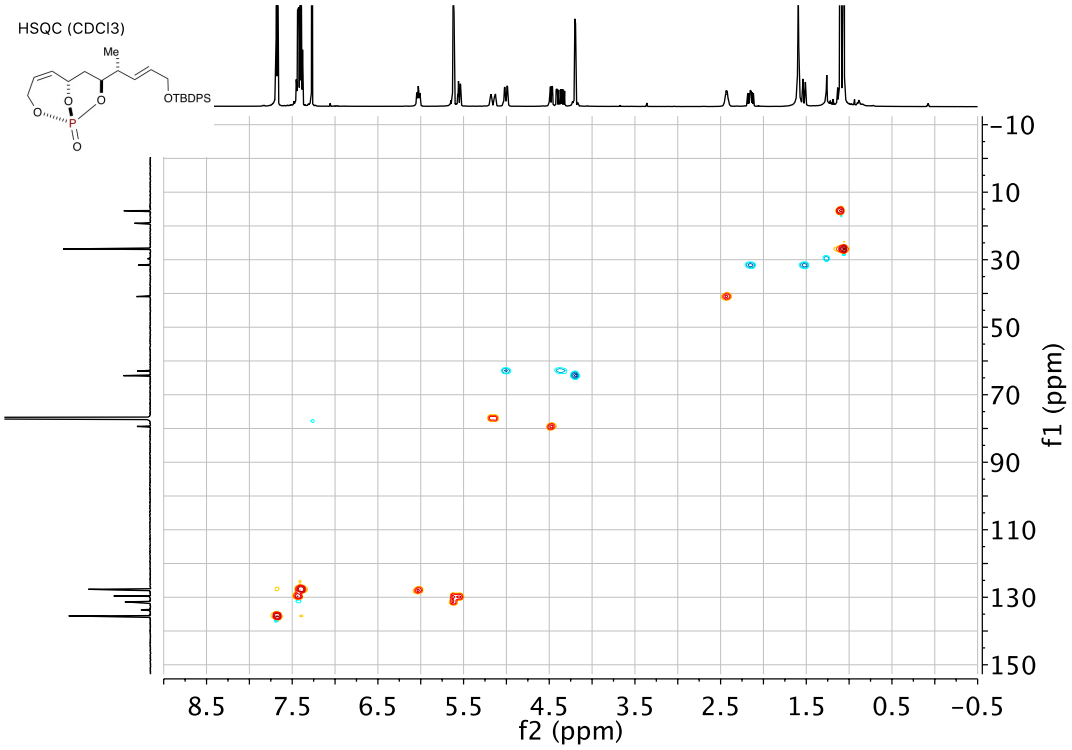
**(1*R*,6*S*,8*S*)-8-((*R*,*E*)-5-((*tert*-butyldiphenylsilyl)oxy)pent-3-en-2-yl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-oxide ($C_{27}H_{35}O_5PSi$, 3.14.6-SI)**

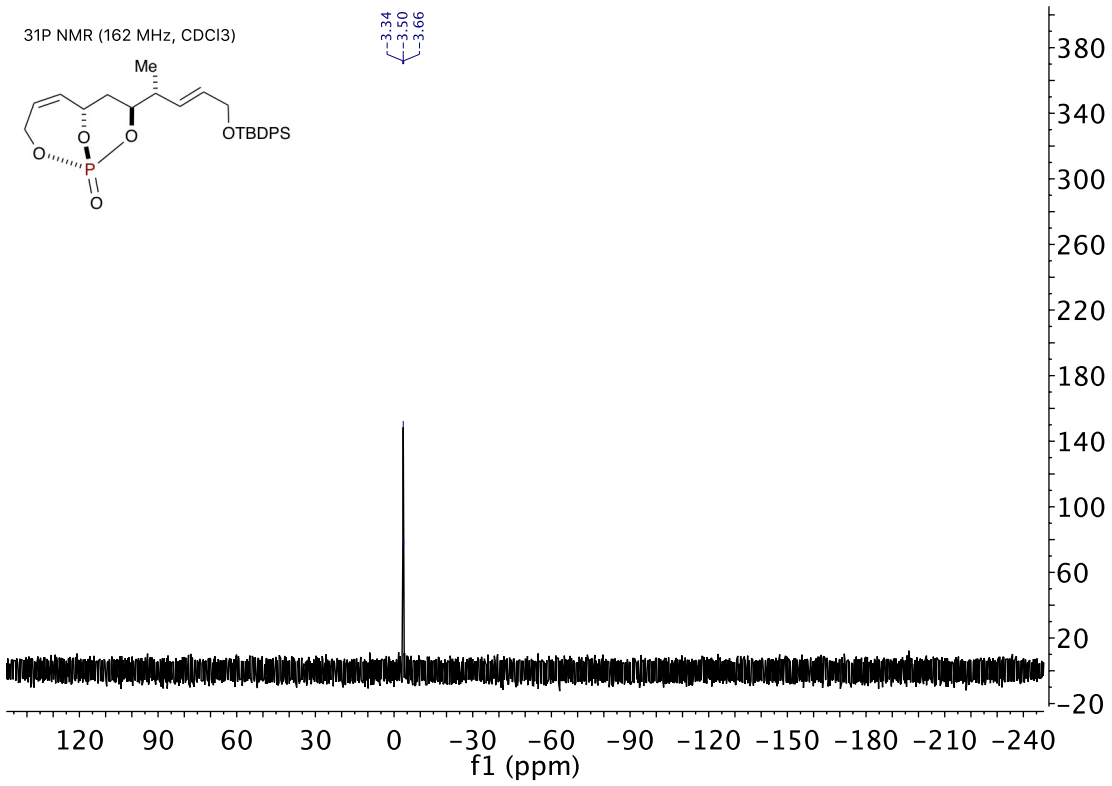



13C NMR (126 MHz, CDCl3)
Me
OTBDPS
135.53
133.70
133.66
131.37
129.89
129.80
129.65
127.91
127.64
127.63
79.45
79.39
77.25
77.05
77.00
76.75
64.34
62.98
62.93
40.92
40.85
31.68
31.63
26.82
19.22
15.49
f1 (ppm)

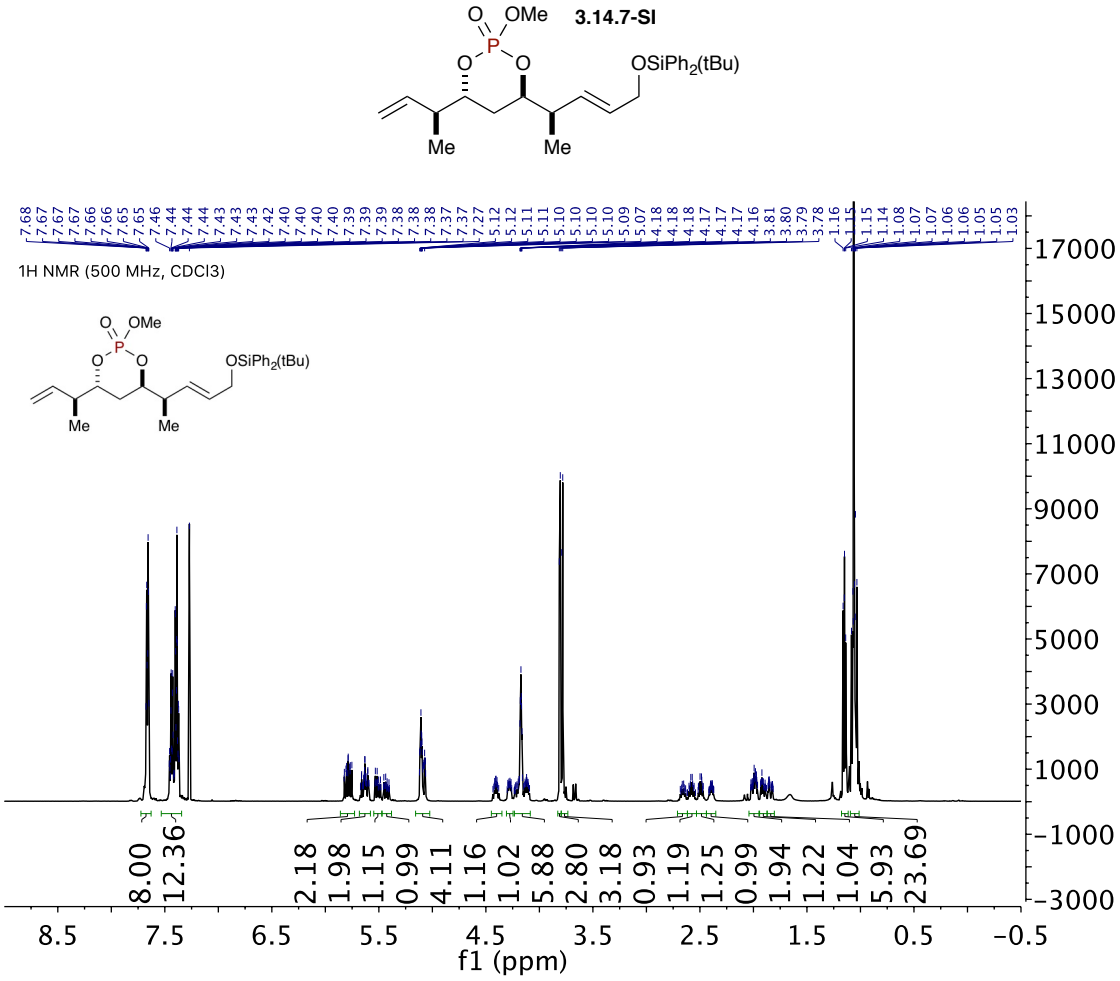

13C NMR {1H} (126 MHz, CDCl3)
Me
OTBDPS
135.56
131.40
129.92
129.83
129.68
127.94
127.67
127.66
79.48
79.43
77.23
77.08
77.03
64.37
63.01
62.96
40.95
40.88
31.71
31.66
26.86
15.52
f1 (ppm)

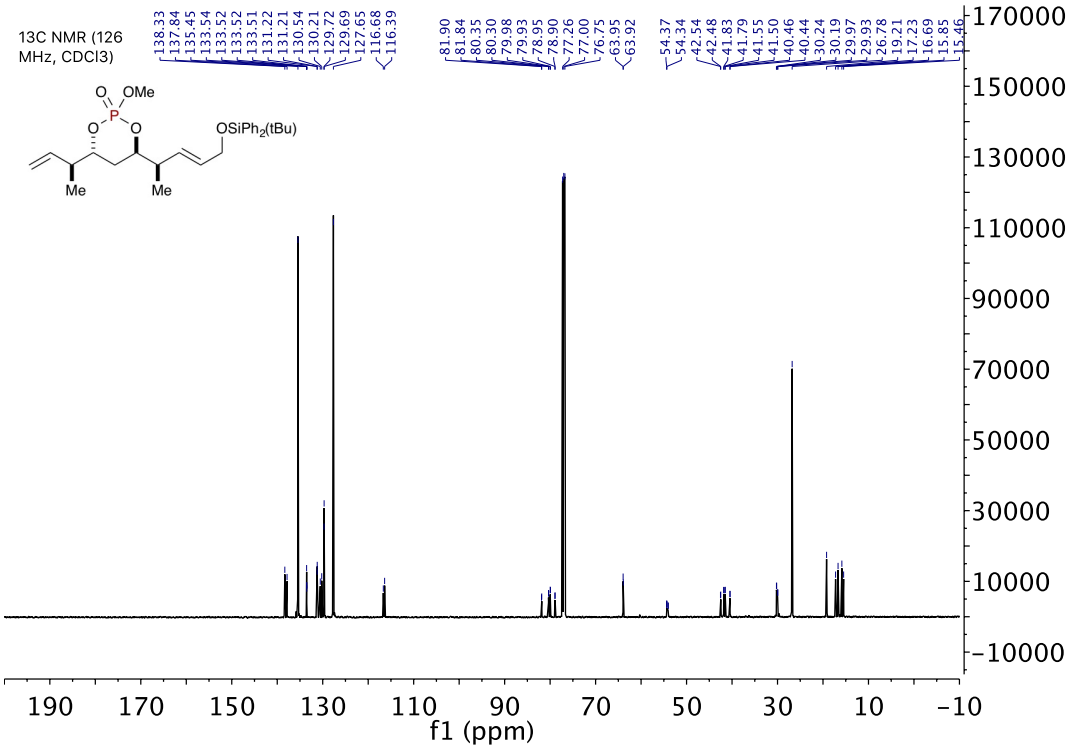

COSY (CDCl3)
Me
OTBDPS
O
O
O
P
O
0
1
2
3
4
5
6
7
8
9
f1 (ppm)
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f2 (ppm)

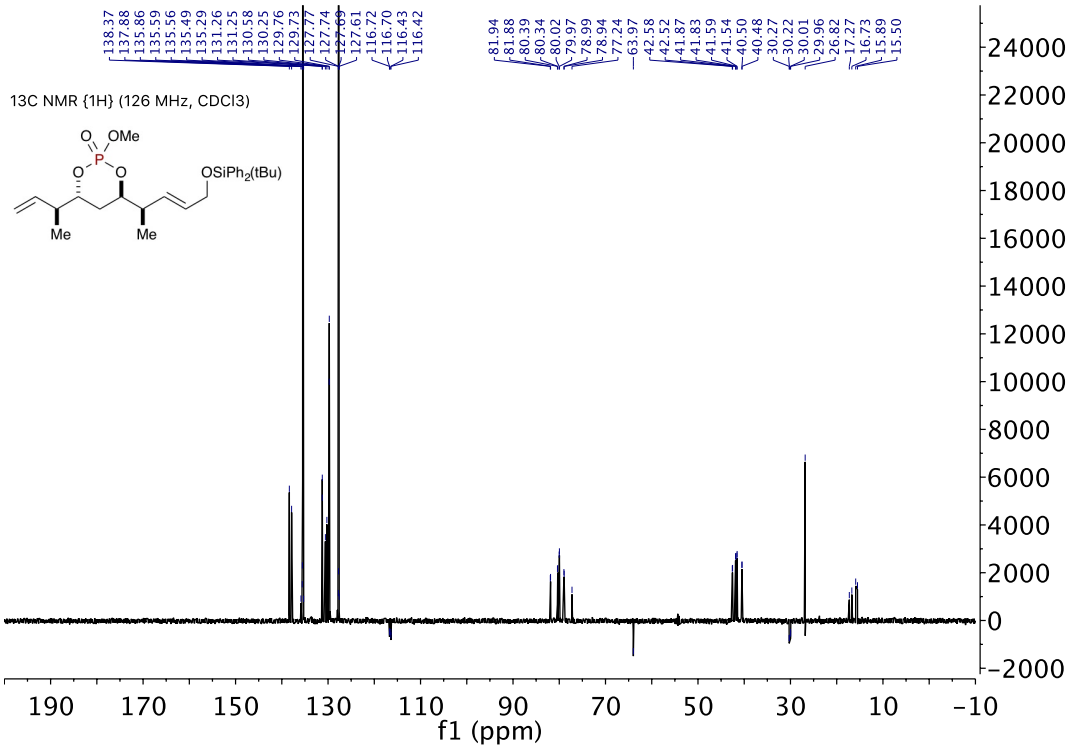

HSQC (CDCl3)
Me
OTBDPS
O
O
O
P
O
-10
10
30
50
70
90
110
130
150
f1 (ppm)
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f2 (ppm)

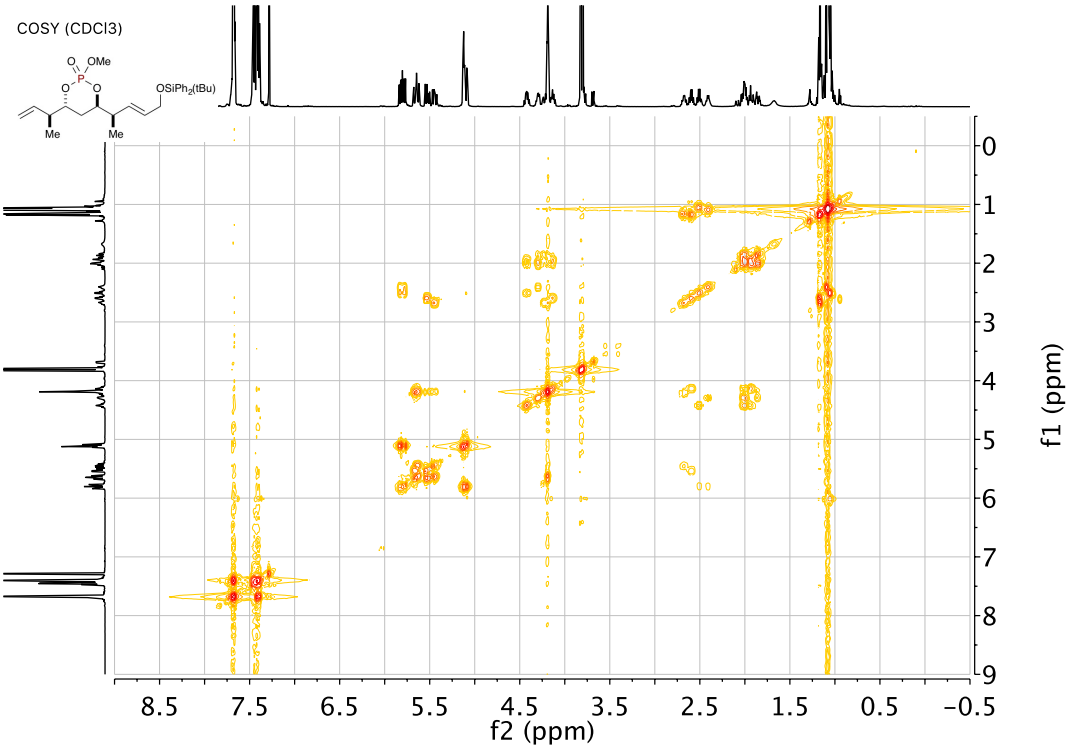

31P NMR (162 MHz, CDCl3)
Me
OTBDPS
O
O
O
P
O
3.34
3.50
3.66
380
340
300
260
220
180
140
100
60
20
-20
120
90
60
30
0
-30
-60
-90
-120
-150
-180
-210
-240
f1 (ppm)

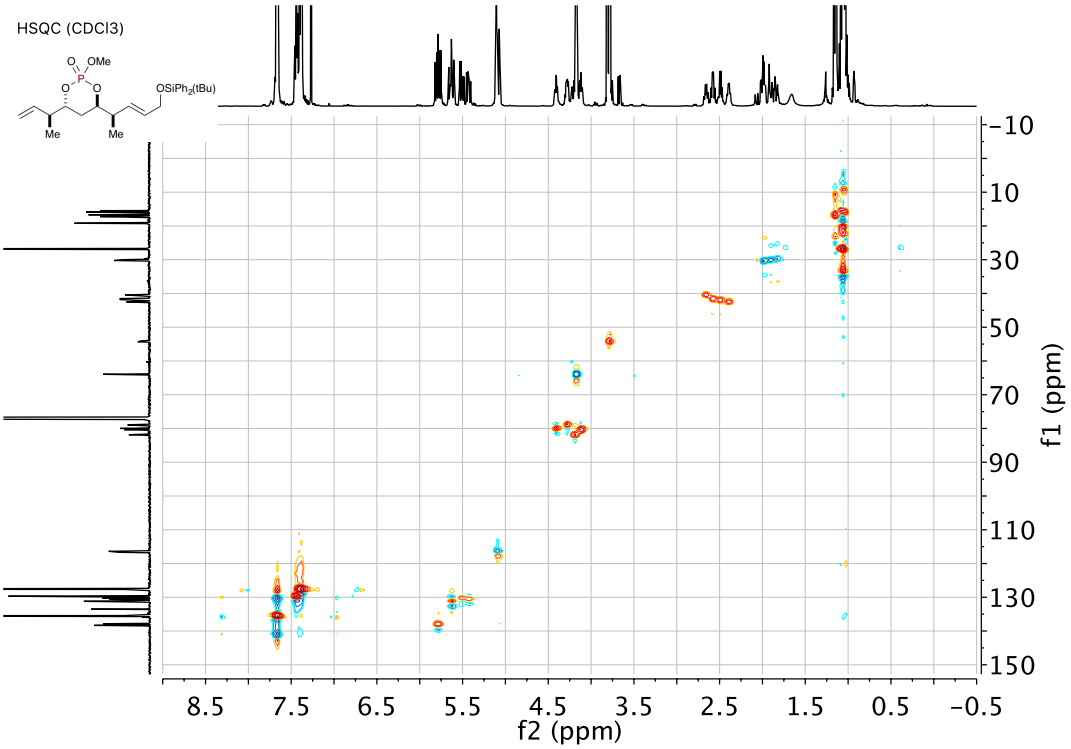
**(4*R*,6*R*)-4-((*S*)-but-3-en-2-yl)-6-((*R*,*E*)-5-((*tert*-butyldiphenylsilyl)oxy)pent-3-en-2-yl)-2-methoxy-1,3,2-dioxaphosphinane 2-oxide ($C_{29}H_{41}O_5PSi$, 3.14.7-SI)**

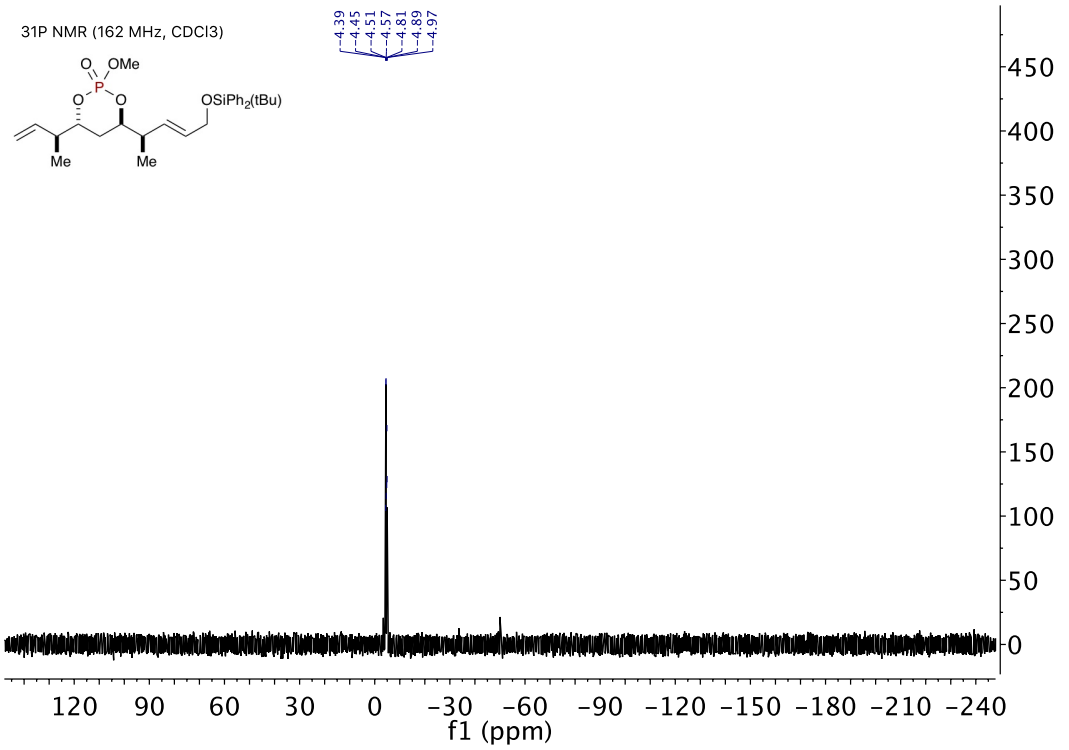


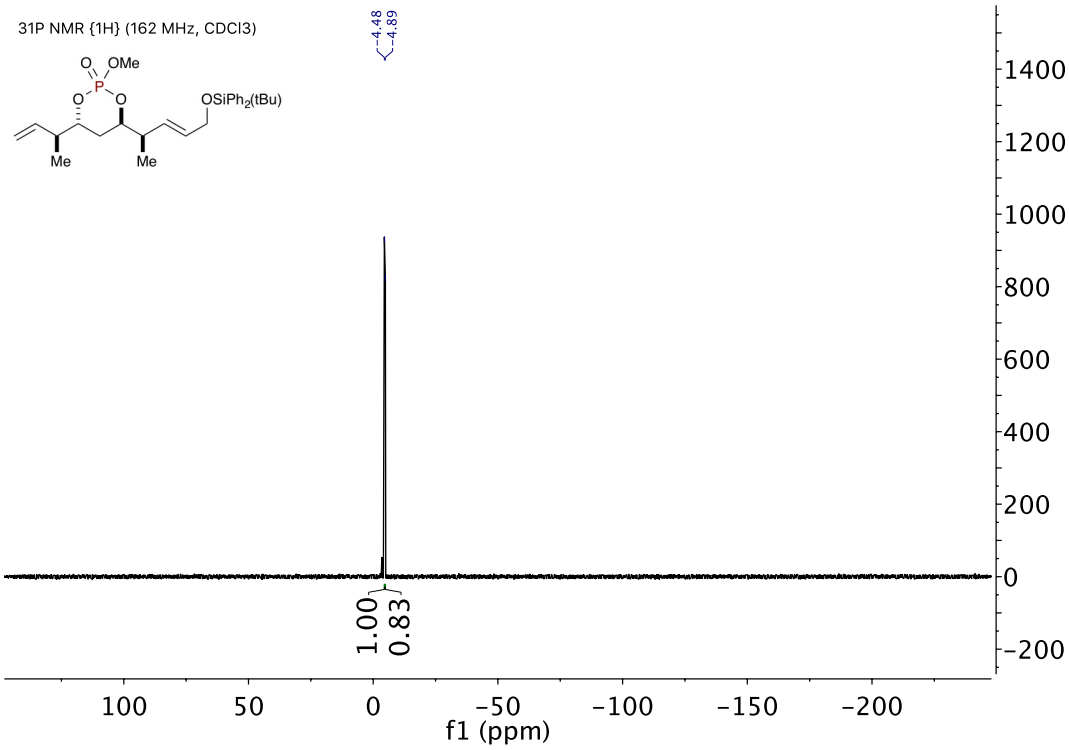

13C NMR (126 MHz, CDCl3)
OMe
OSiPh2(tBu)
Me
Me
f1 (ppm)


13C NMR {1H} (126 MHz, CDCl3)
OMe
OSiPh2(tBu)
Me
Me
f1 (ppm)

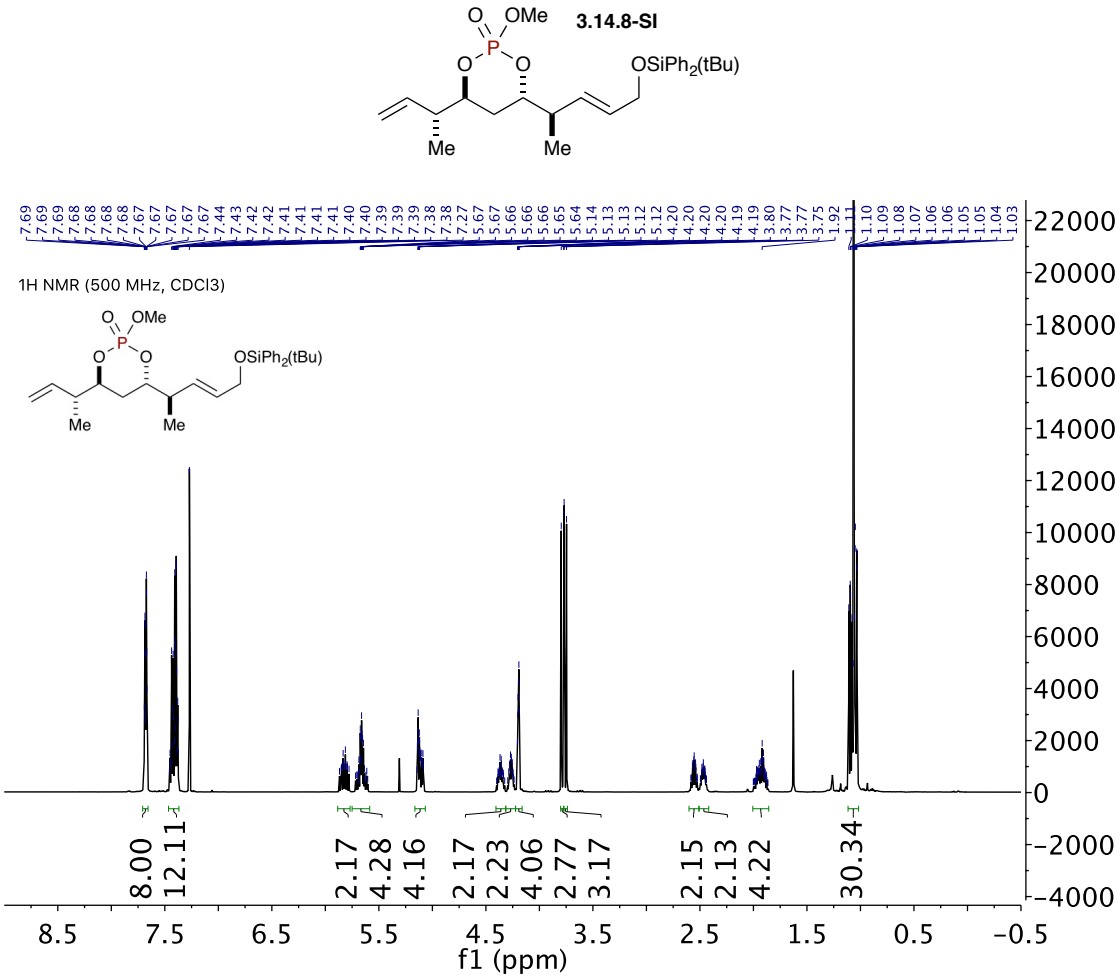

COSY (CDCl3)
OMe
OSiPh2(tBu)
Me
Me
f1 (ppm)
f2 (ppm)

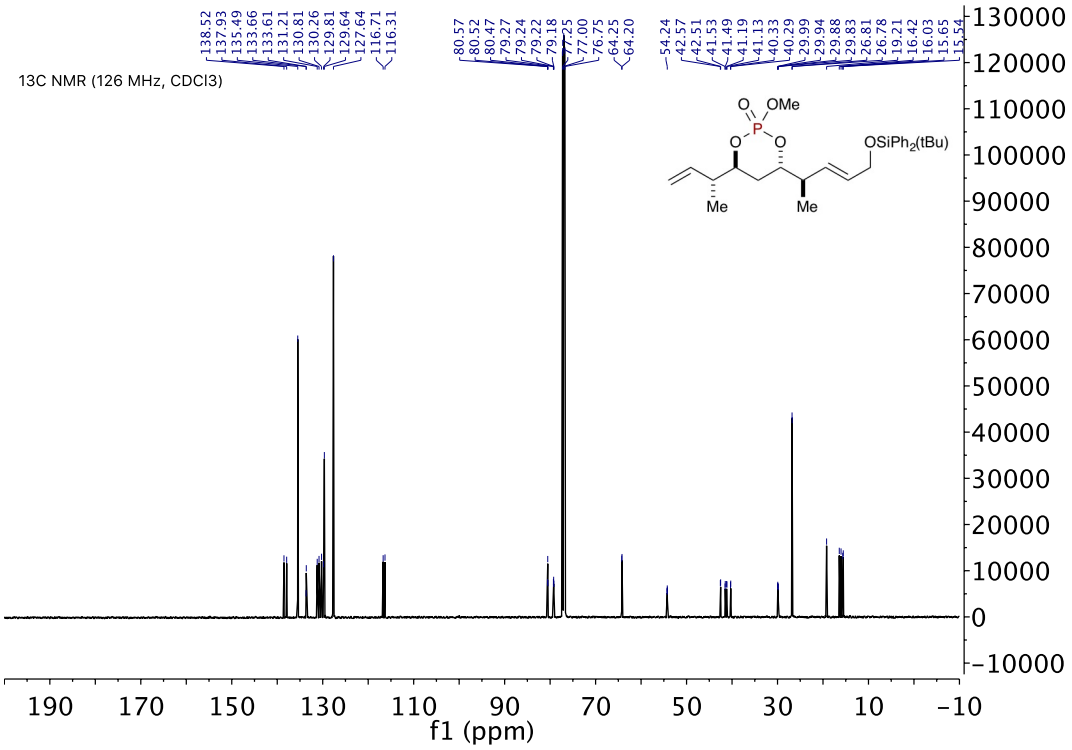

HSQC (CDCl3)
OMe
OSiPh2(tBu)
Me
Me
f1 (ppm)
f2 (ppm)

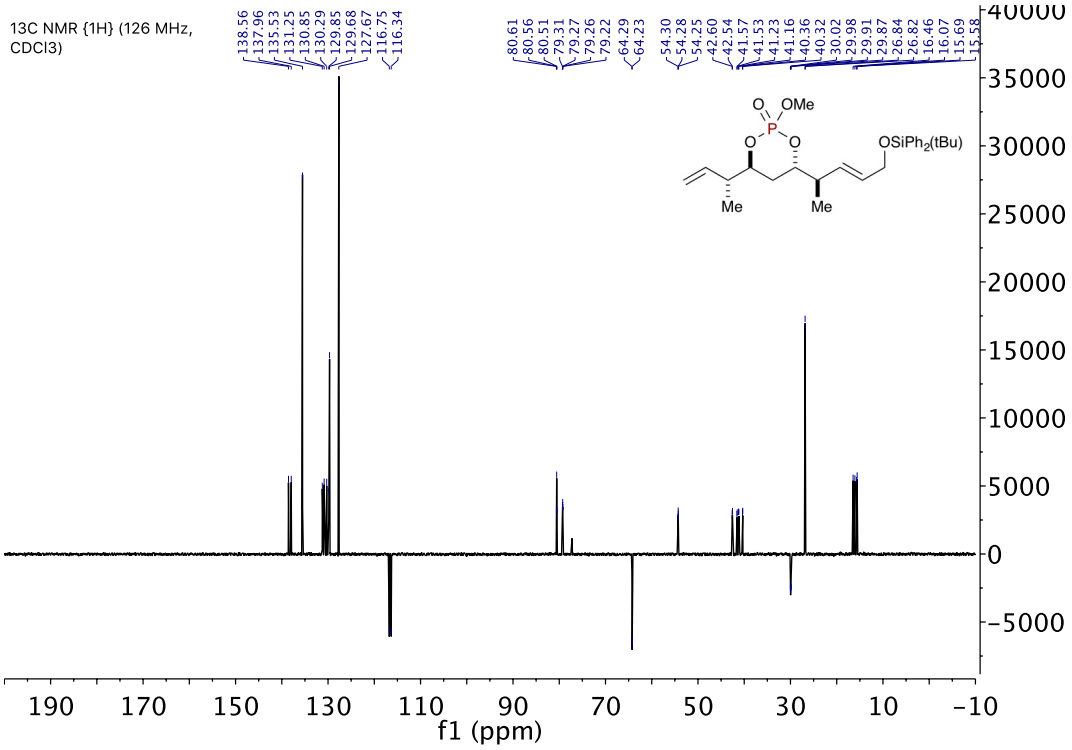

31P NMR (162 MHz, CDCl3)
4.39
4.45
4.51
4.57
4.81
4.89
4.97
OMe
OSiPh2(tBu)
Me
Me
450
400
350
300
250
200
150
100
50
0
120 90 60 30 0 -30 -60 -90 -120 -150 -180 -210 -240
f1 (ppm)

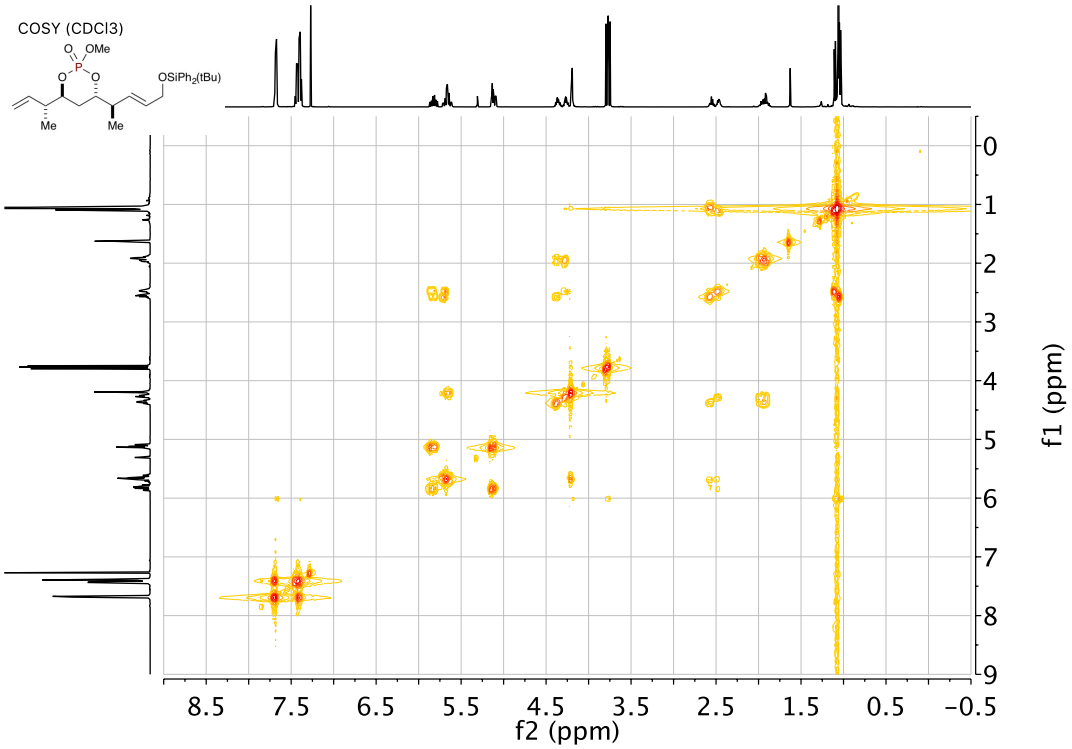

31P NMR {1H} (162 MHz, CDCl3)
4.48
4.89
OMe
OSiPh2(tBu)
Me
Me
1400
1200
1000
800
600
400
200
0
-200
1.00
0.83
100 50 0 -50 -100 -150 -200
f1 (ppm)

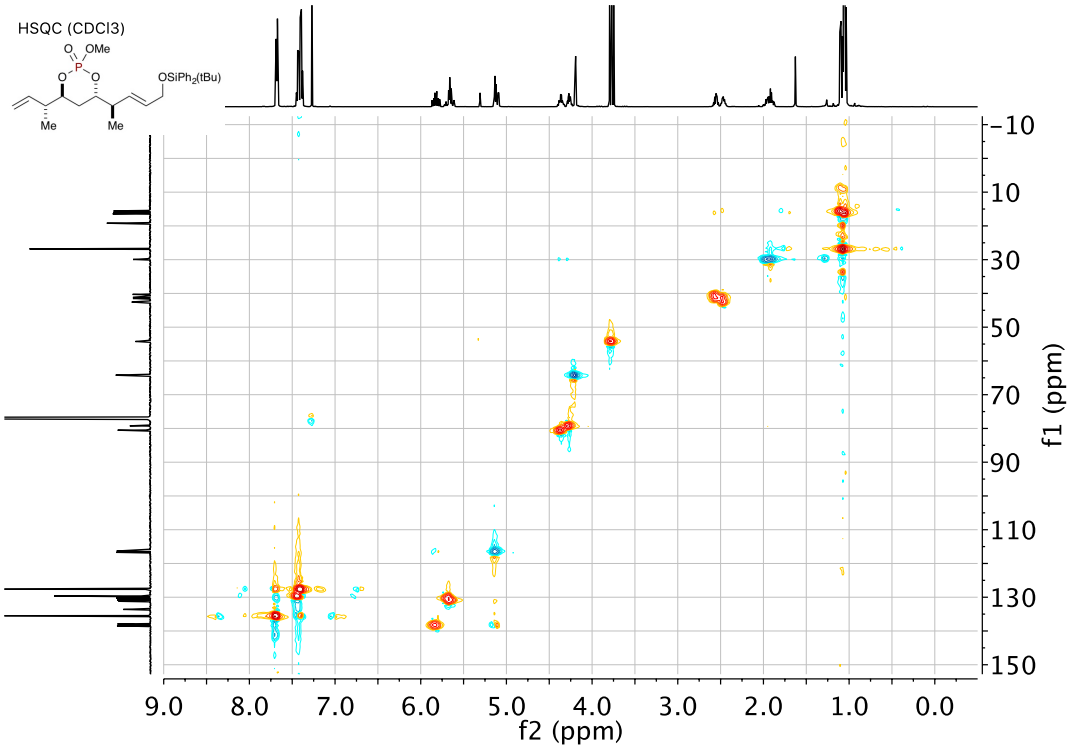
**(4*S*,6*S*)-4-((*R*)-but-3-en-2-yl)-6-((*R*,*E*)-5-((*tert*-butyldiphenylsilyl)oxy)pent-3-en-2-yl)-2-methoxy-1,3,2-dioxaphosphinane 2-oxide ($C_{29}H_{41}O_5PSi$, 3.14.8-SI)**

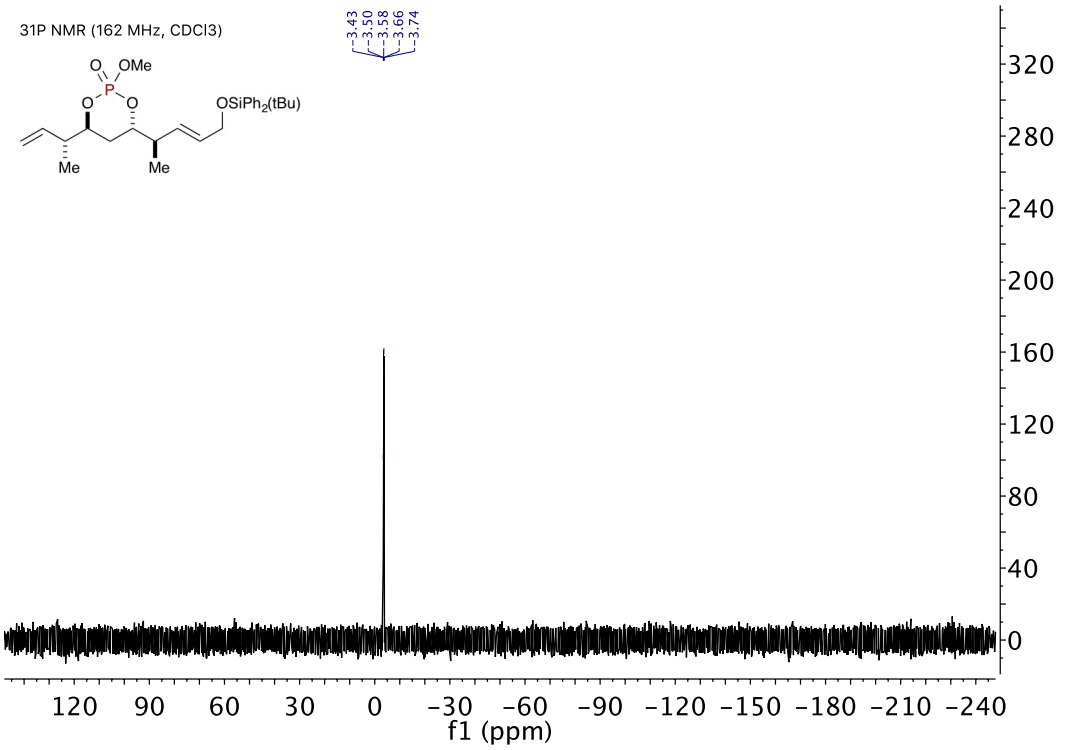


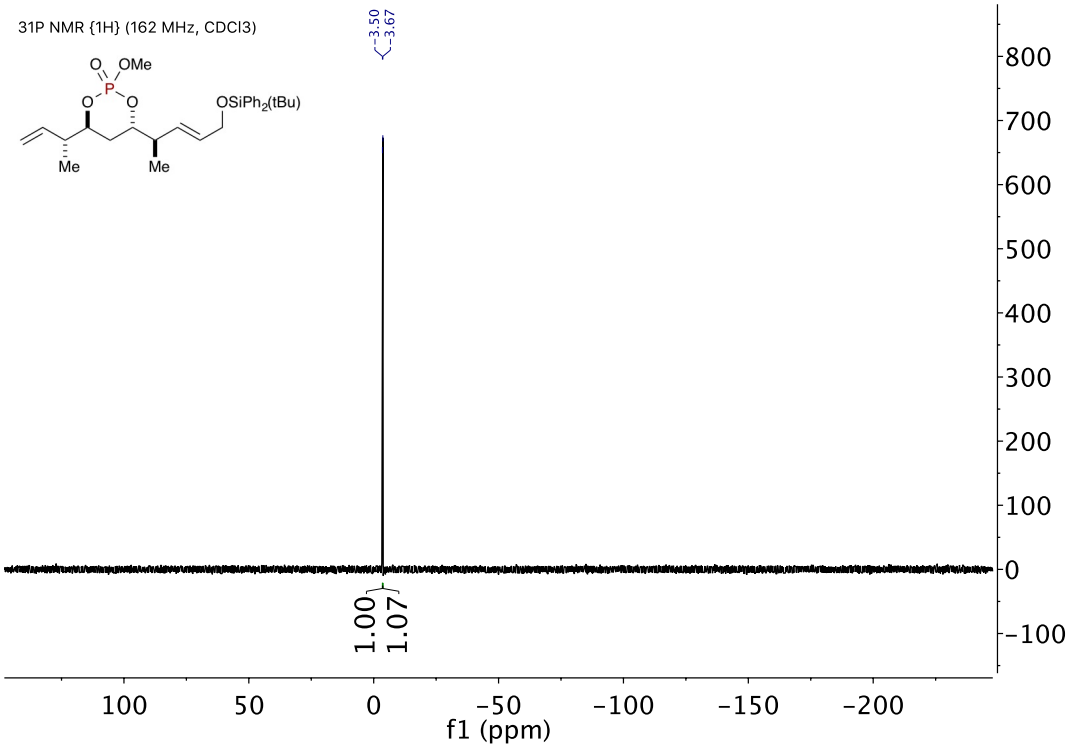

13C NMR (126 MHz, CDCl3)
138.52
137.93
135.49
133.66
133.61
131.21
130.81
130.26
129.81
129.64
127.64
116.71
116.31
80.57
80.52
80.47
79.27
79.24
79.22
79.18
77.25
77.00
76.75
64.25
64.20
54.24
42.57
42.51
41.53
41.49
41.19
41.13
40.33
40.29
29.99
29.94
29.88
29.83
26.81
26.78
19.21
16.42
16.03
15.65
15.54
OMe
OSiPh2(tBu)
Me
Me
f1 (ppm)


13C NMR {1H} (126 MHz, CDCl3)
138.56
137.96
135.53
131.25
130.85
130.29
129.85
129.68
127.67
116.75
116.34
80.61
80.56
80.51
79.31
79.27
79.26
79.22
64.29
64.23
54.30
54.28
54.25
42.60
42.54
41.57
41.53
41.23
41.16
40.36
40.32
30.02
29.98
29.91
29.87
26.84
26.82
16.46
16.07
15.69
15.58
OMe
OSiPh2(tBu)
Me
Me
f1 (ppm)

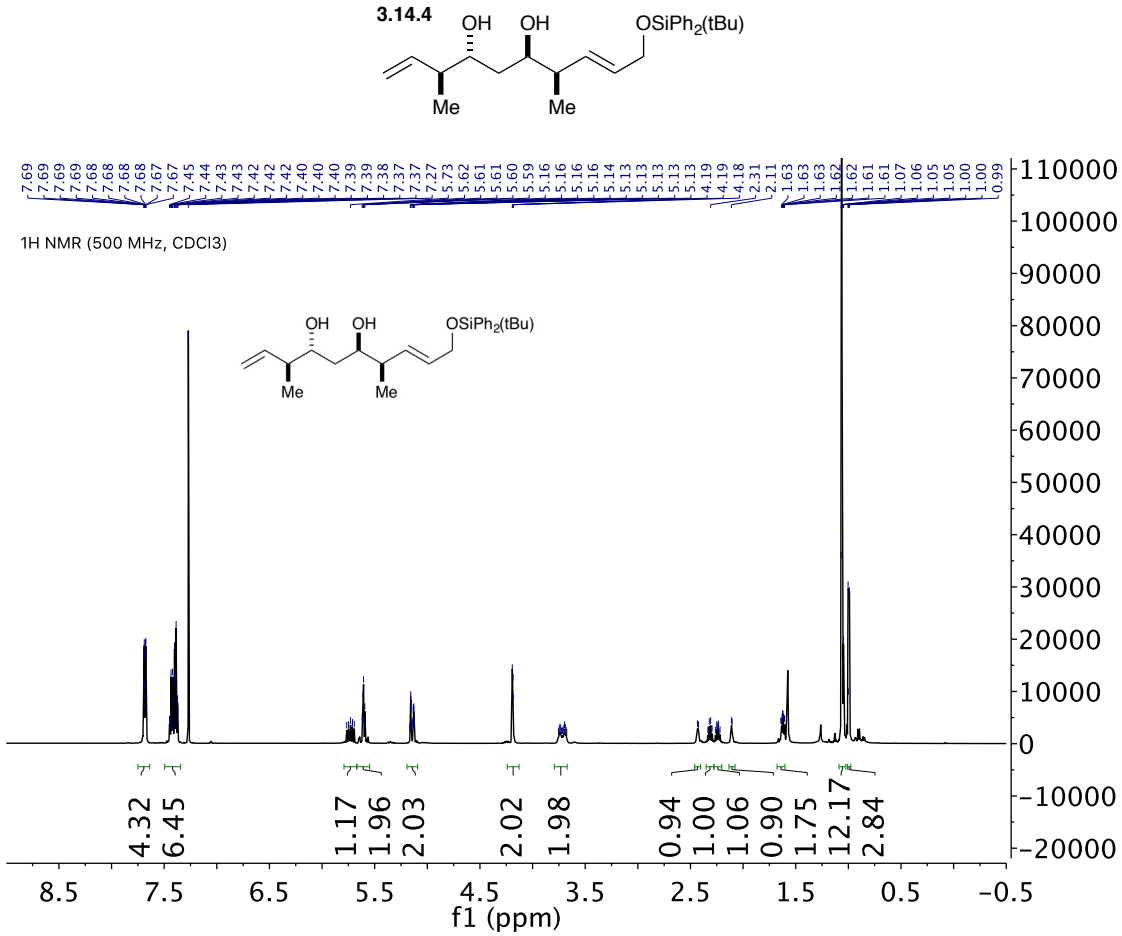

COSY (CDCl3)
OMe
OSiPh2(tBu)
Me
Me
f1 (ppm)
f2 (ppm)

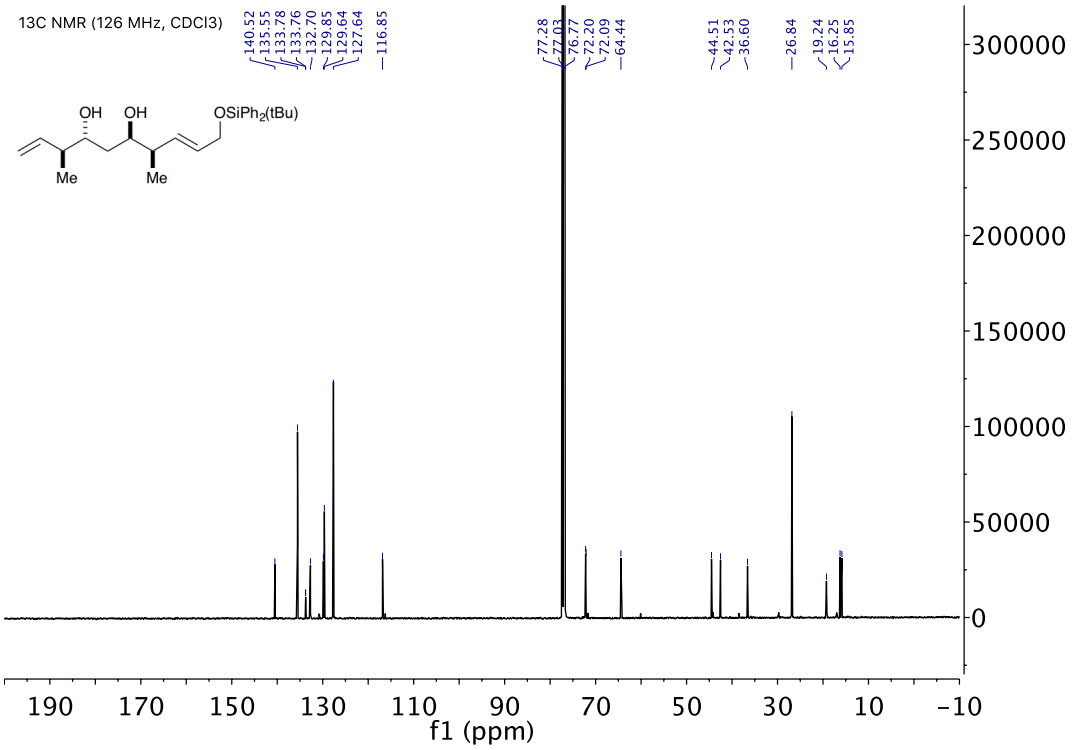

HSQC (CDCl3)
OMe
OSiPh2(tBu)
Me
Me
f1 (ppm)
f2 (ppm)

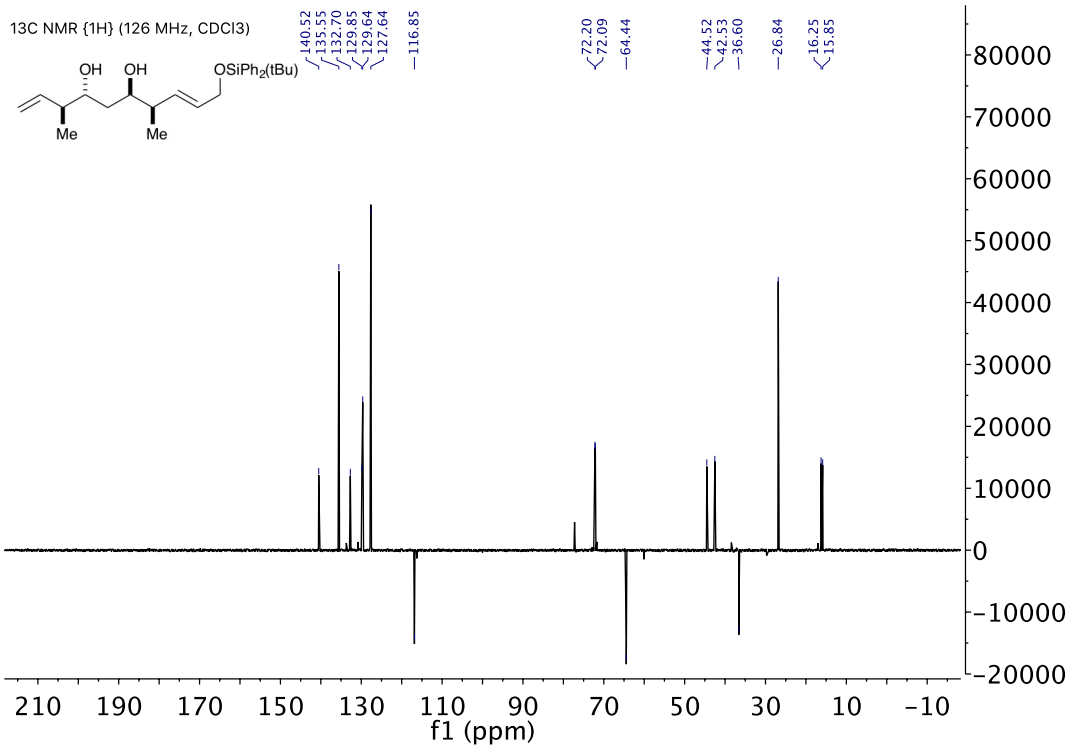

31P NMR (162 MHz, CDCl3)
3.43
3.50
3.58
3.66
3.74
OMe
OSiPh2(tBu)
Me
Me
320
280
240
200
160
120
80
40
0
120 90 60 30 0 -30 -60 -90 -120 -150 -180 -210 -240
f1 (ppm)

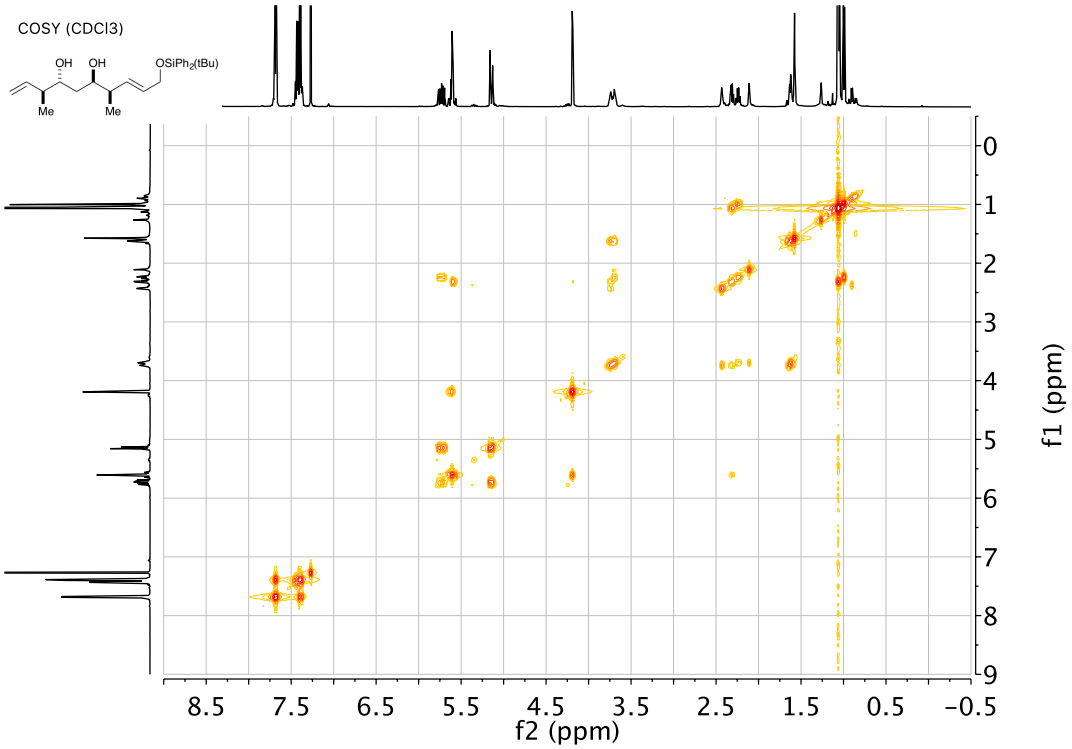

31P NMR {1H} (162 MHz, CDCl3)
3.50
3.67
OMe
OSiPh2(tBu)
Me
Me
800
700
600
500
400
300
200
100
0
-100
1.00
1.07
100 50 0 -50 -100 -150 -200
f1 (ppm)

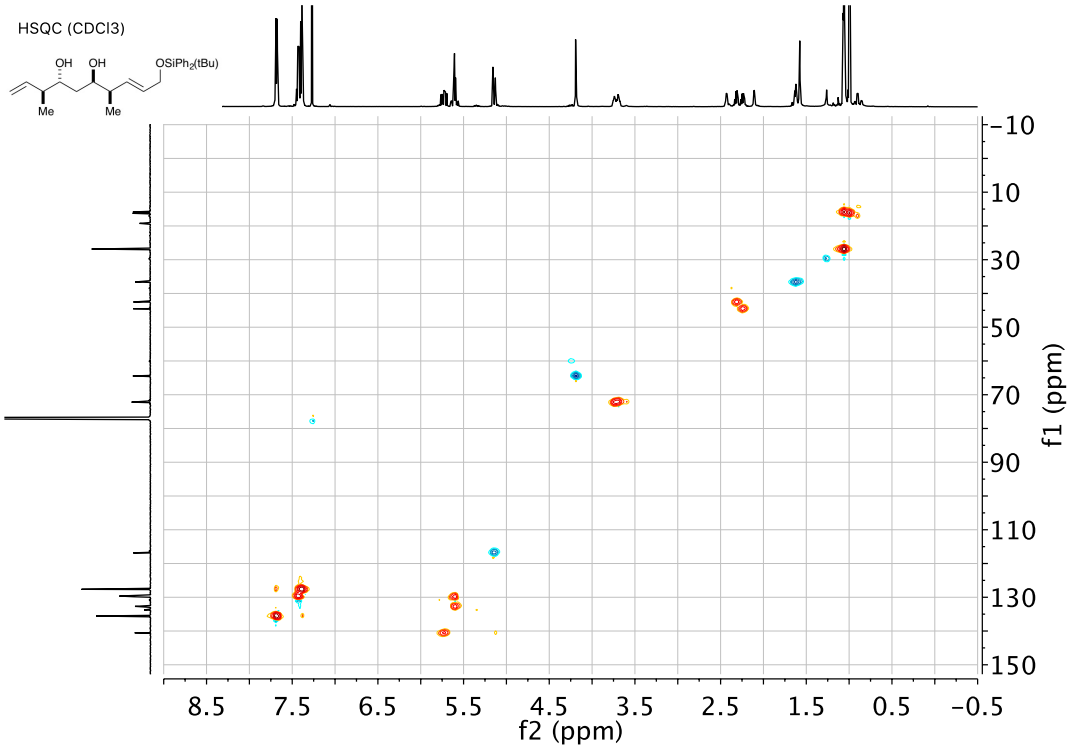
**(3*S*,4*R*,6*R*,7*R*,*E*)-10-((*tert*-butyldiphenylsilyl)oxy)-3,7-dimethyldeca-1,8-diene-4,6-diol ($C_{28}H_{40}O_3Si$, 3.14.4)**



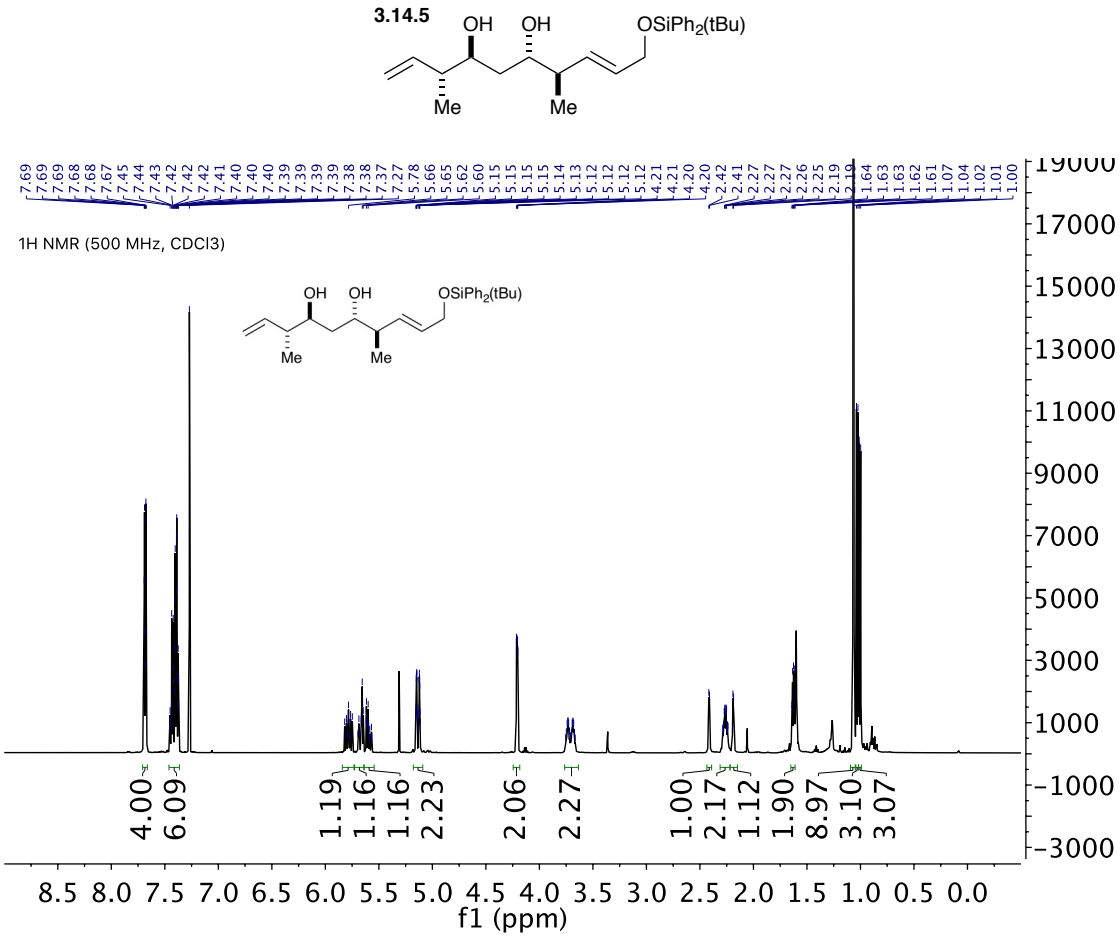

13C NMR (126 MHz, CDCl3)
140.52
135.55
133.78
133.76
132.70
129.85
129.64
127.64
116.85
77.28
77.03
76.77
72.20
72.09
64.44
44.51
42.53
36.60
26.84
19.24
16.25
15.85
OH
OH
OSiPh2(tBu)
Me
Me
300000
250000
200000
150000
100000
50000
0
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

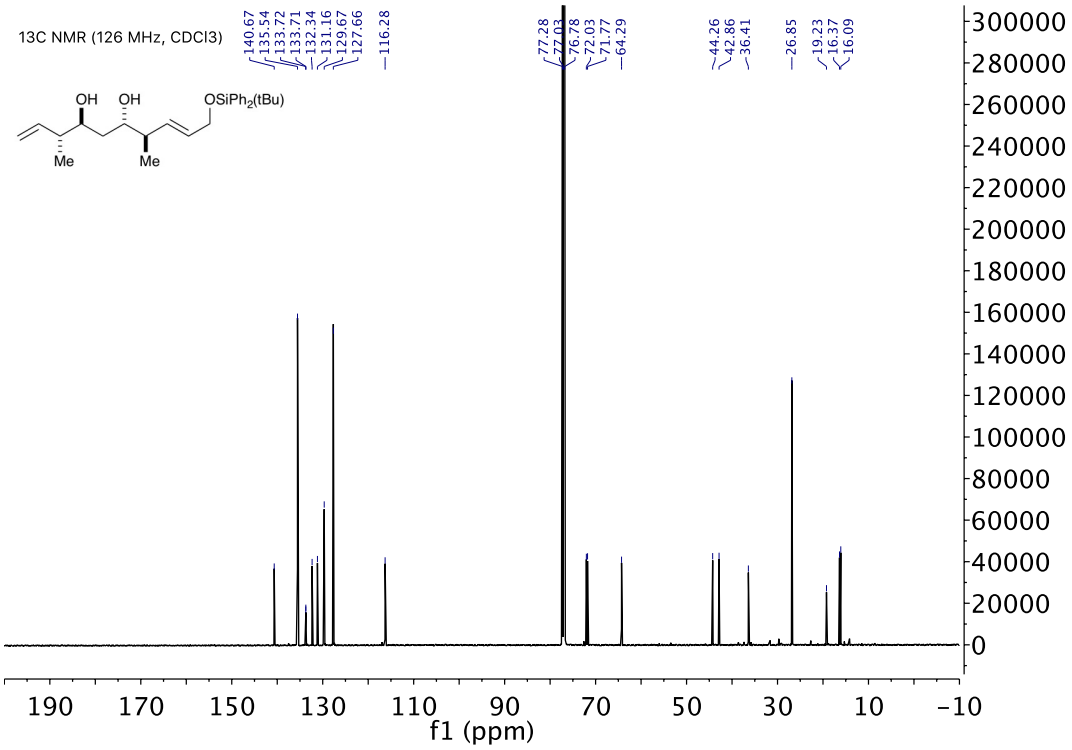

13C NMR {1H} (126 MHz, CDCl3)
140.52
135.55
132.70
129.85
129.64
127.64
116.85
72.20
72.09
64.44
44.52
42.53
36.60
26.84
16.25
15.85
OH
OH
OSiPh2(tBu)
Me
Me
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
-20000
210
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)

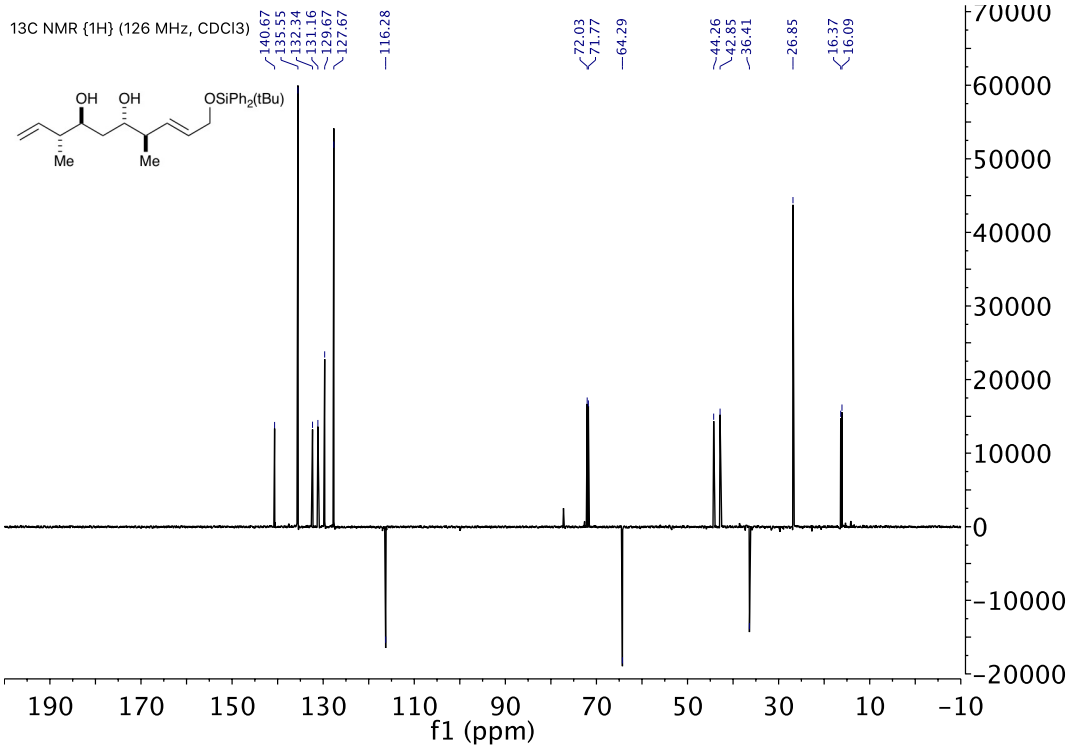

COSY (CDCl3)
OH
OH
OSiPh2(tBu)
Me
Me
f2 (ppm)
f1 (ppm)

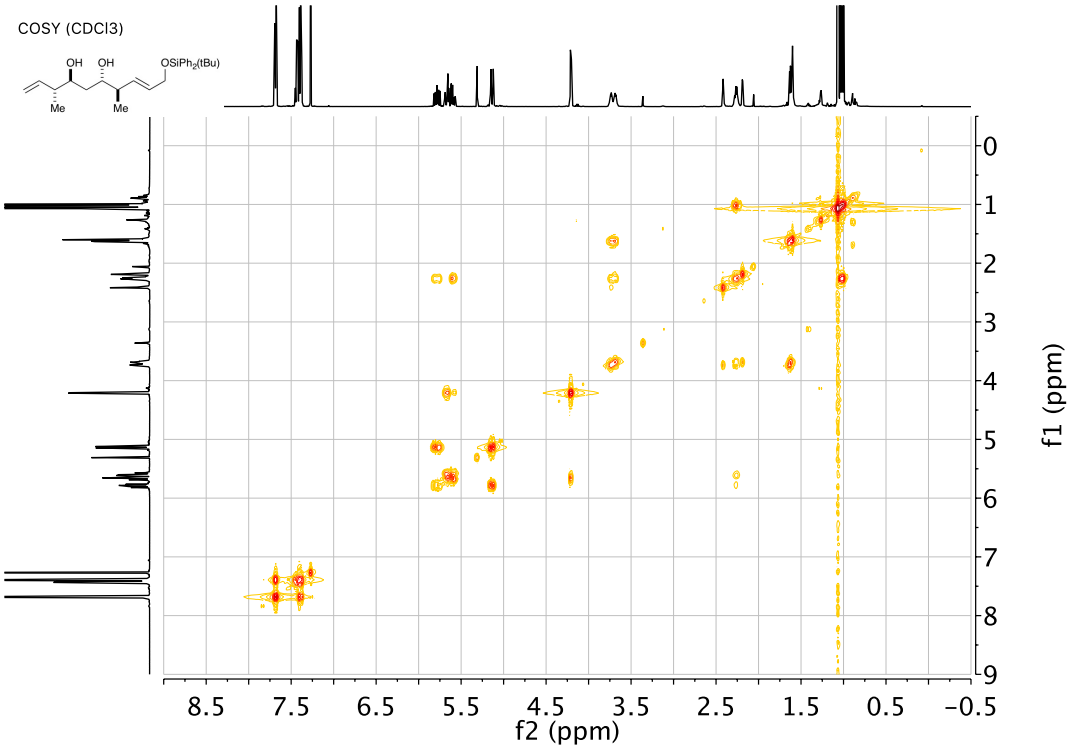

HSQC (CDCl3)
OH
OH
OSiPh2(tBu)
Me
Me
f2 (ppm)
f1 (ppm)

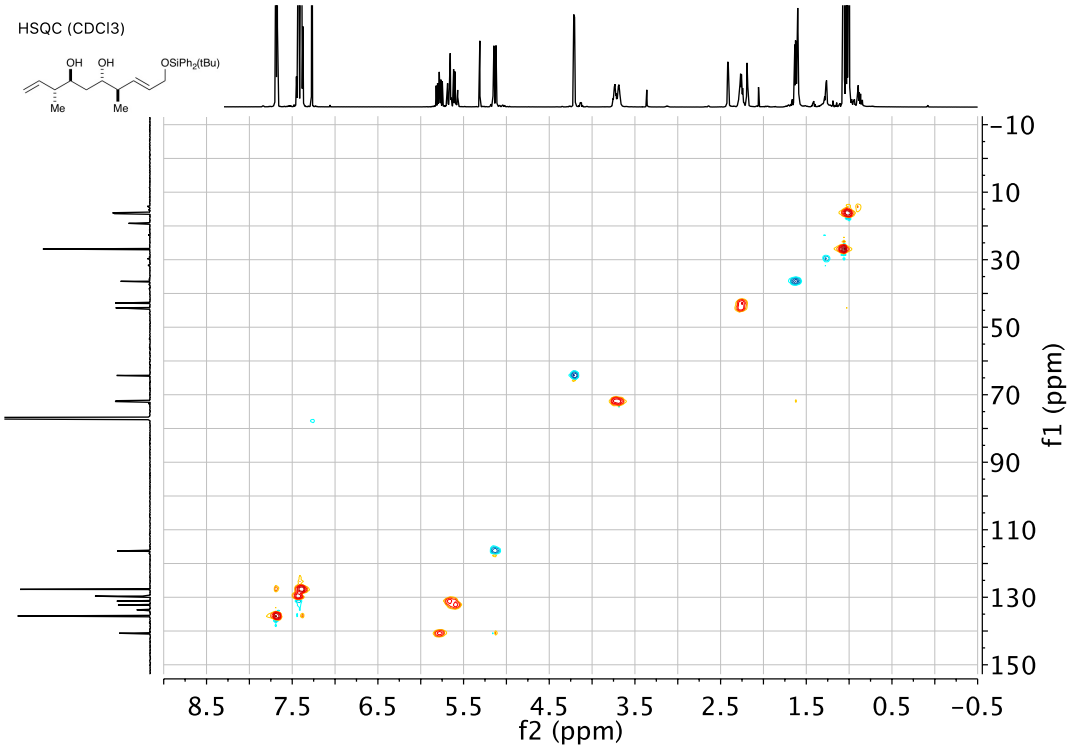
**(3*R*,4*S*,6*S*,7*R*,*E*)-10-((*tert*-butyldiphenylsilyl)oxy)-3,7-dimethyldeca-1,8-diene-4,6-diol ($C_{28}H_{40}O_3Si$, 3.14.5)**



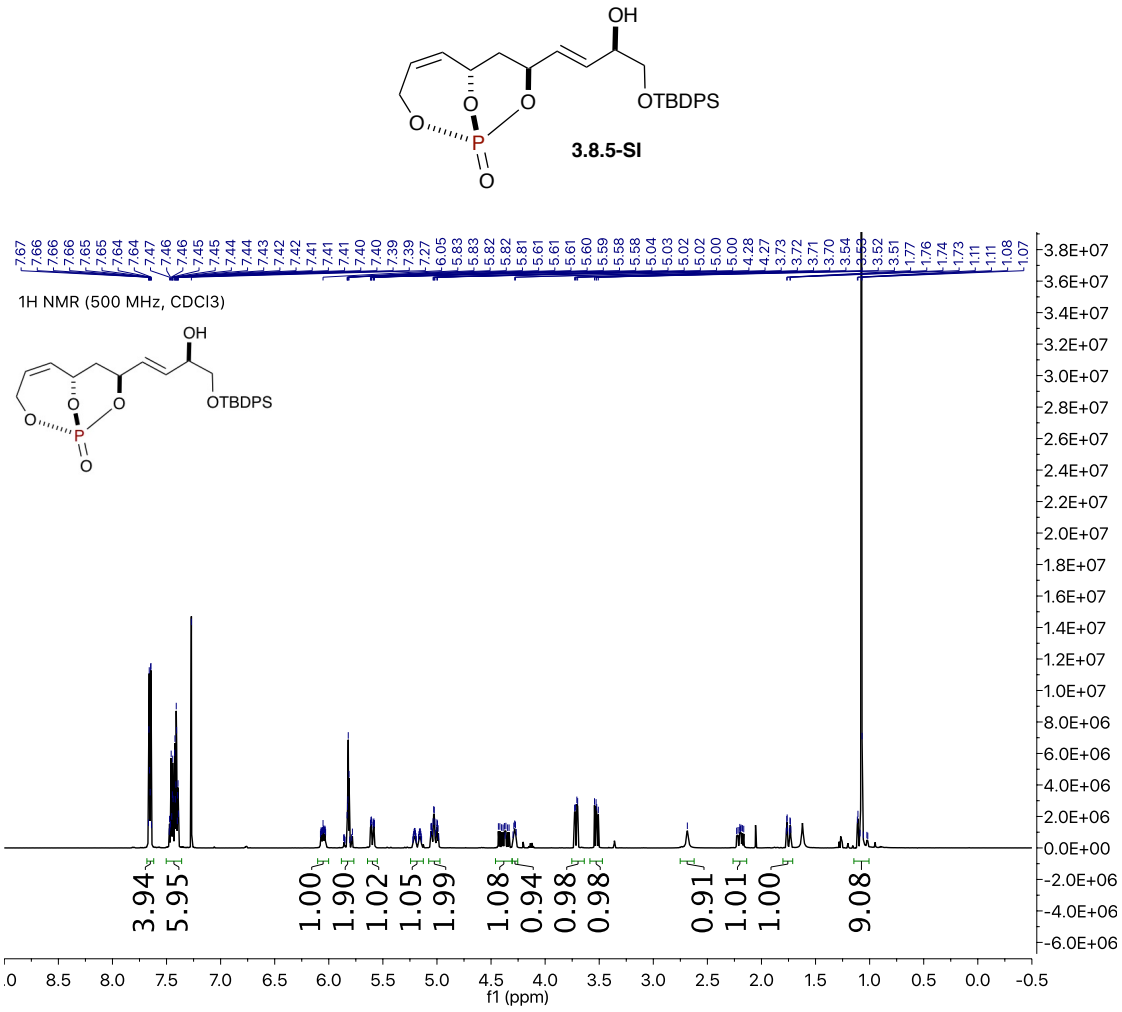

13C NMR (126 MHz, CDCl3)
140.67
135.54
133.72
133.71
132.34
131.16
129.67
127.66
116.28
77.28
77.03
76.78
72.03
71.77
64.29
44.26
42.86
36.41
26.85
19.23
16.37
16.09
OH
OH
OSiPh2(tBu)
Me
Me
f1 (ppm)

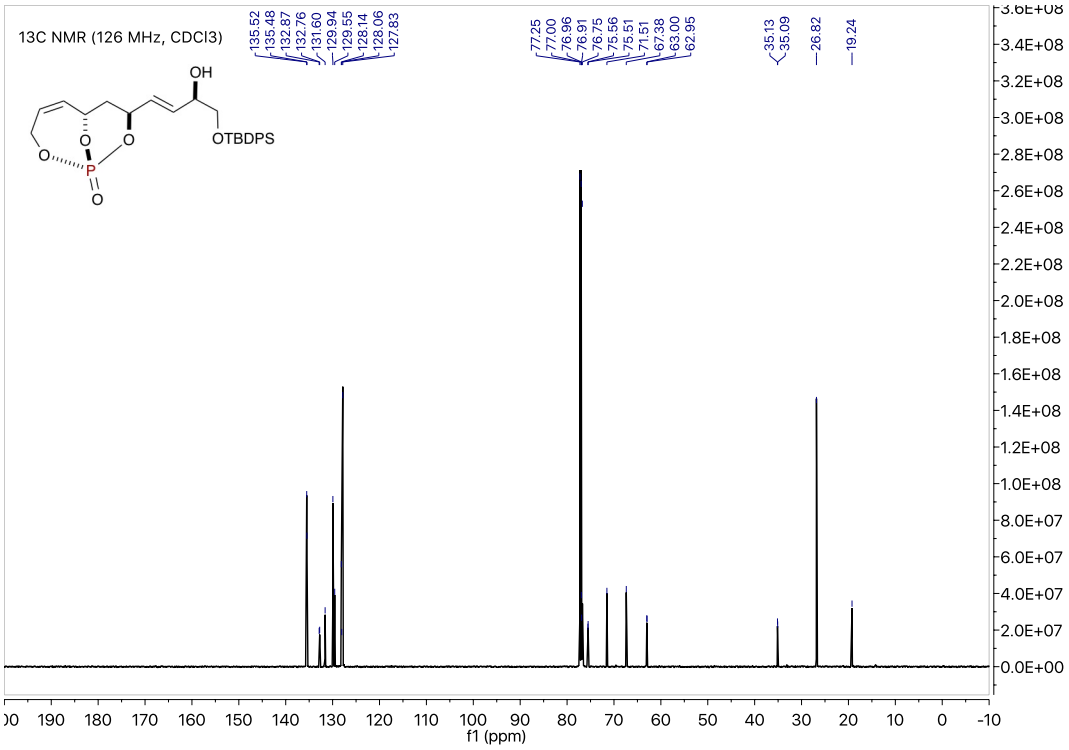

13C NMR {1H} (126 MHz, CDCl3)
140.67
135.55
132.34
131.16
129.67
127.67
116.28
72.03
71.77
64.29
44.26
42.85
36.41
26.85
16.37
16.09
OH
OH
OSiPh2(tBu)
Me
Me
f1 (ppm)

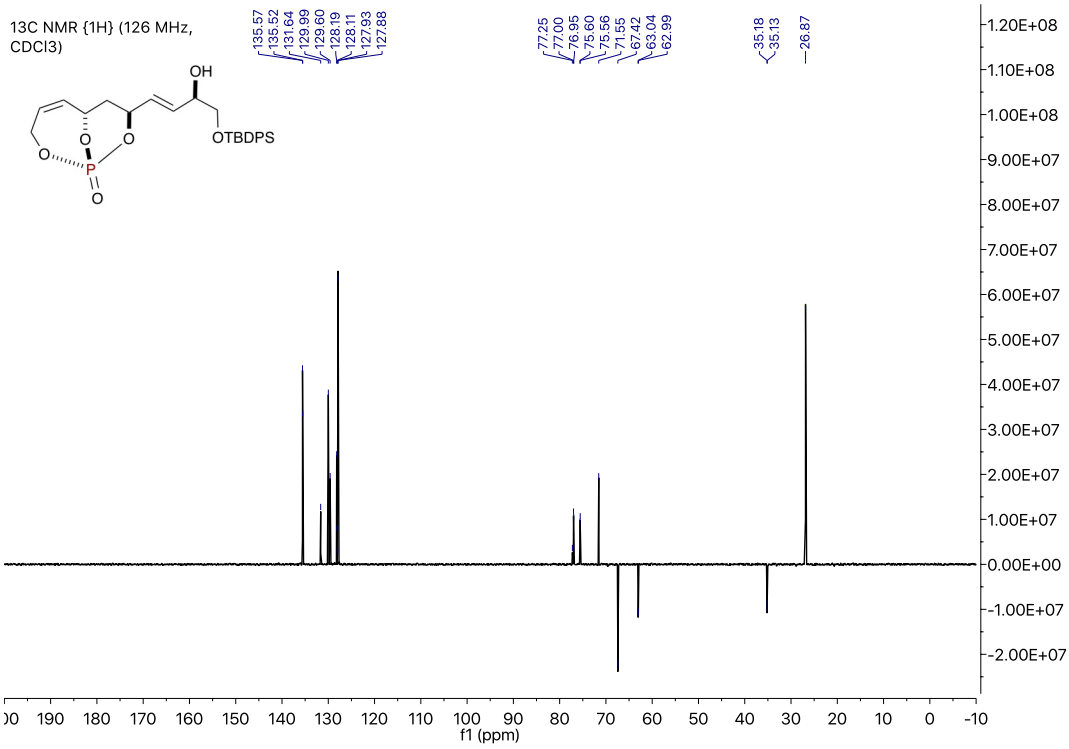

COSY (CDCl3)
OH
OH
OSiPh2(tBu)
Me
Me
0
1
2
3
4
5
6
7
8
9
f1 (ppm)
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f2 (ppm)

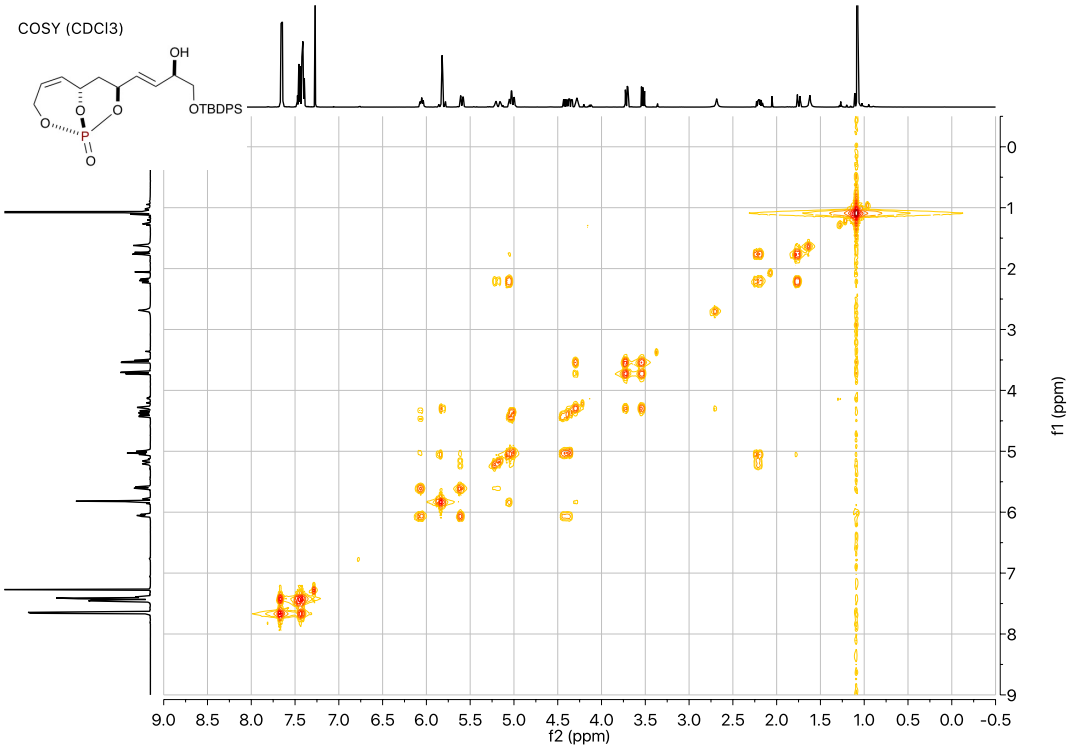

HSQC (CDCl3)
OH
OH
OSiPh2(tBu)
Me
Me
-10
10
30
50
70
90
110
130
150
f1 (ppm)
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f2 (ppm)

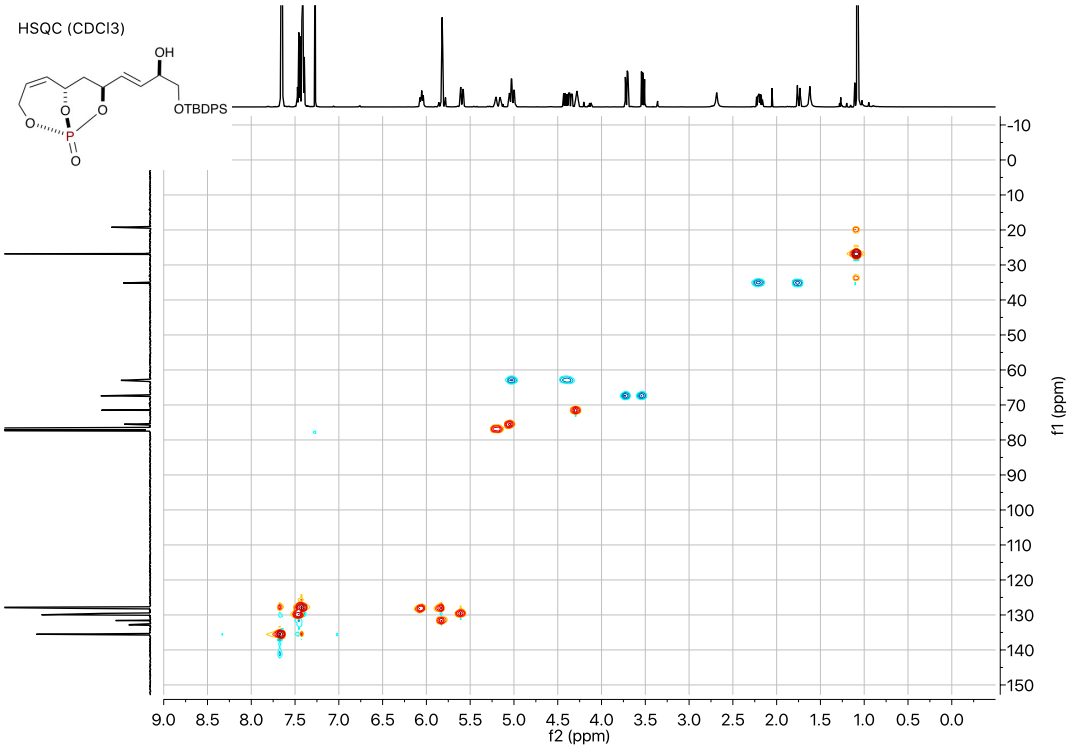
**(1*R*,6*S*,8*S*)-8-((*R*,*E*)-4-((*tert*-butyldiphenylsilyl)oxy)-3-hydroxybut-1-en-1-yl)-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-ene 1-oxide ($C_{26}H_{33}O_6PSi$, 3.8.5-SI)**

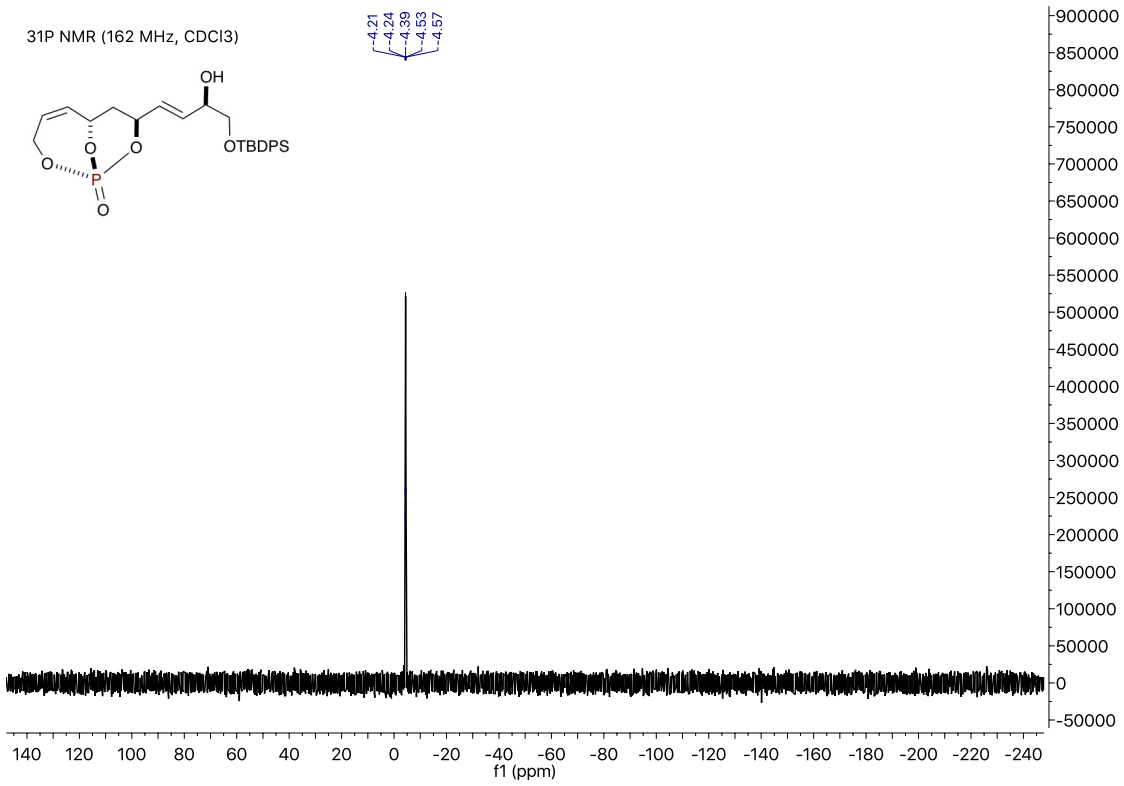



13C NMR (126 MHz, CDCl3)
135.52
135.48
132.87
132.76
131.60
129.94
129.55
128.14
128.06
127.83
77.25
77.00
76.96
76.91
76.75
75.56
75.51
71.51
67.38
63.00
62.95
35.13
35.09
26.82
19.24
OH
OTBDPS
O
O
O
P
O
f1 (ppm)

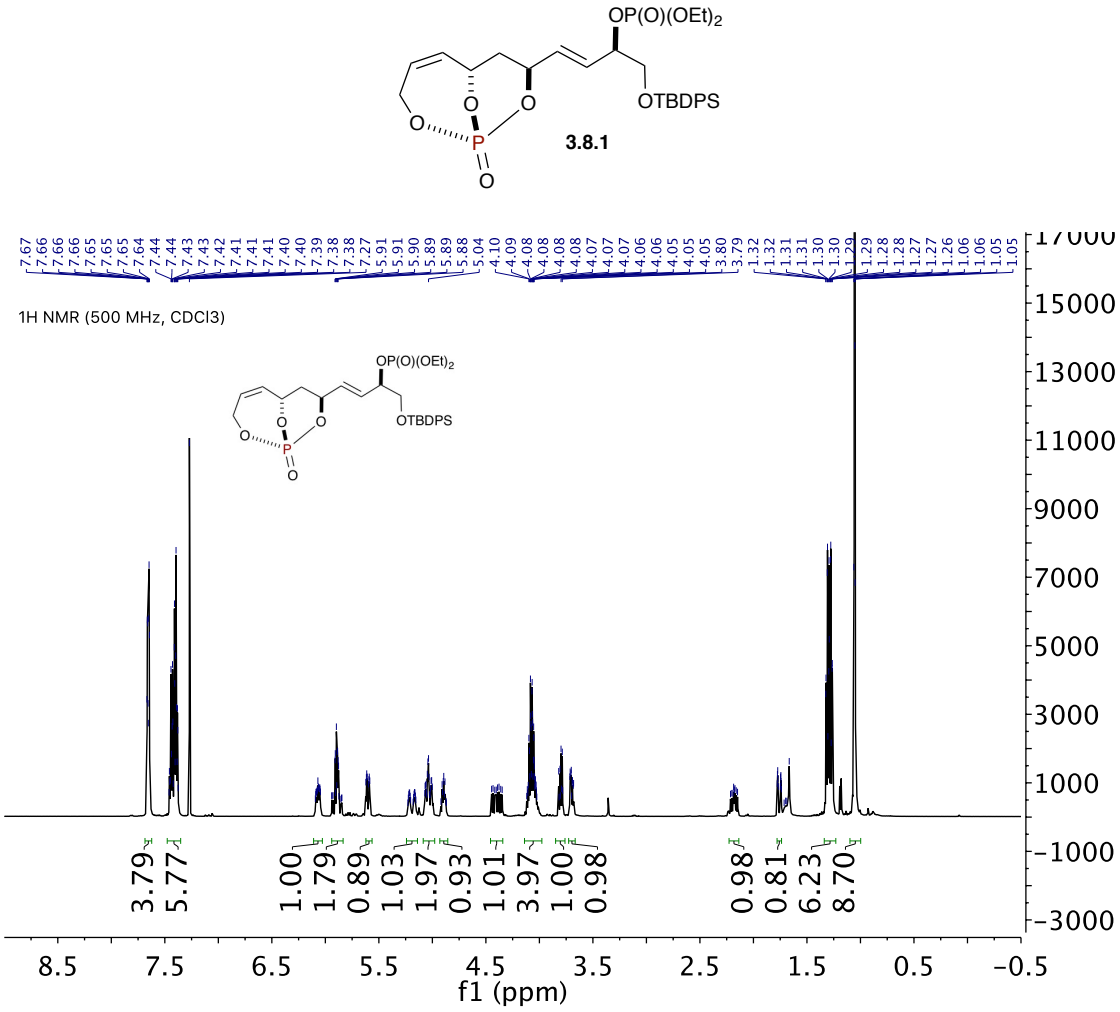

13C NMR {1H} (126 MHz, CDCl3)
135.57
135.52
131.64
129.99
129.60
128.19
128.11
127.93
127.88
77.25
77.00
76.95
75.60
75.56
71.55
67.42
63.04
62.99
35.18
35.13
26.87
OH
OTBDPS
O
O
O
P
O
f1 (ppm)

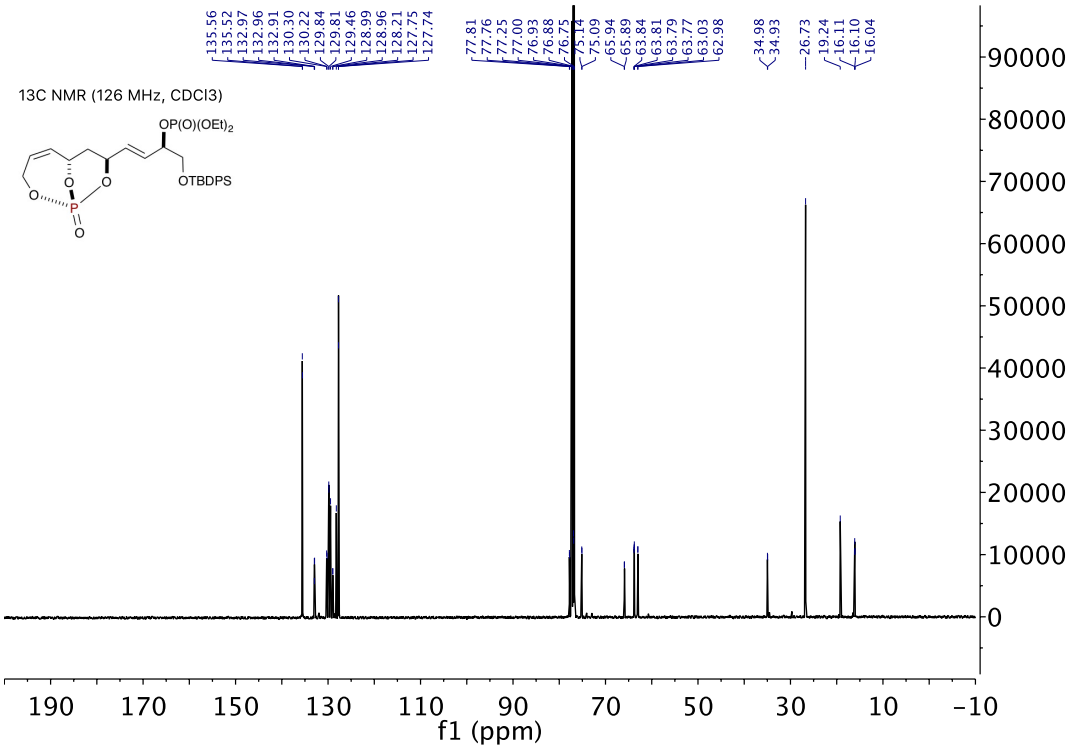

COSY (CDCl3)
OH
OTBDPS
O
O
O
P
O
f2 (ppm)
f1 (ppm)

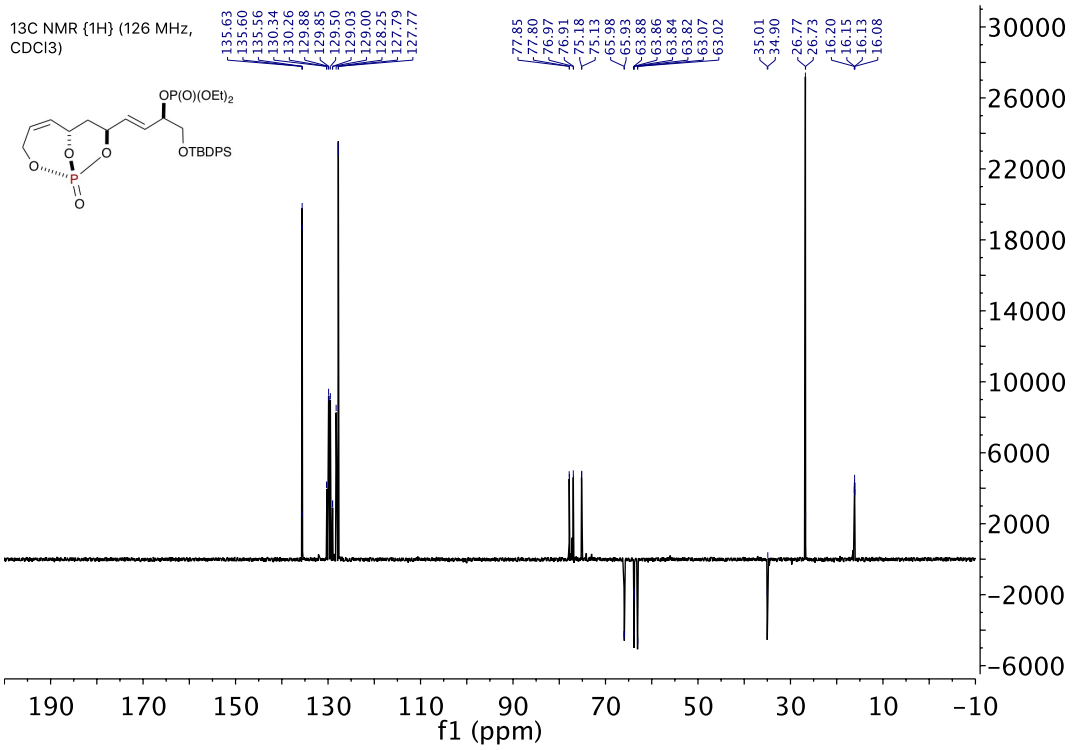

HSQC (CDCl3)
OH
OTBDPS
O
O
O
P
O
f2 (ppm)
f1 (ppm)


31P NMR (162 MHz, CDCl3)
4.21
4.24
4.39
4.53
4.57
OH
OTBDPS
O
O
O
P
O
900000
850000
800000
750000
700000
650000
600000
550000
500000
450000
400000
350000
300000
250000
200000
150000
100000
50000
0
-50000
140 120 100 80 60 40 20 0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 -220 -240
f1 (ppm)

**(*R*,*E*)-1-((*tert*-butyldiphenylsilyl)oxy)-4-((1*R*,6*S*,8*S*)-1-oxido-2,9,10-trioxa-1-phosphabicyclo[4.3.1]dec-4-en-8-yl)but-3-en-2-yl diethyl phosphate ($C_{30}H_{42}O_9P_2Si$, 3.8.1)**




13C NMR (126 MHz, CDCl3)
OP(O)(OEt)2
OTBDPS
135.56
135.52
132.97
132.96
132.91
130.30
130.22
129.84
129.81
129.46
128.99
128.96
128.21
127.75
127.74
77.81
77.76
77.25
77.00
76.93
76.88
76.75
75.14
75.09
65.94
65.89
63.84
63.81
63.79
63.77
63.03
62.98
34.98
34.93
26.73
19.24
16.11
16.10
16.04
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
190
170
150
130
110
90
70
50
30
10
-10
f1 (ppm)


13C NMR {1H} (126 MHz, CDCl3)
OP(O)(OEt)2
OTBDPS
135.63
135.60
135.56
130.34
130.26
129.88
129.85
129.50
129.03
129.00
128.25
127.79
127.77
77.85
77.80
76.97
76.91
75.18
75.13
65.98
65.93
63.88
63.86
63.84
63.82
63.07
63.02
35.01
34.90
26.77
26.73
16.20
16.15
16.13
16.08
30000
26000
22000
18000
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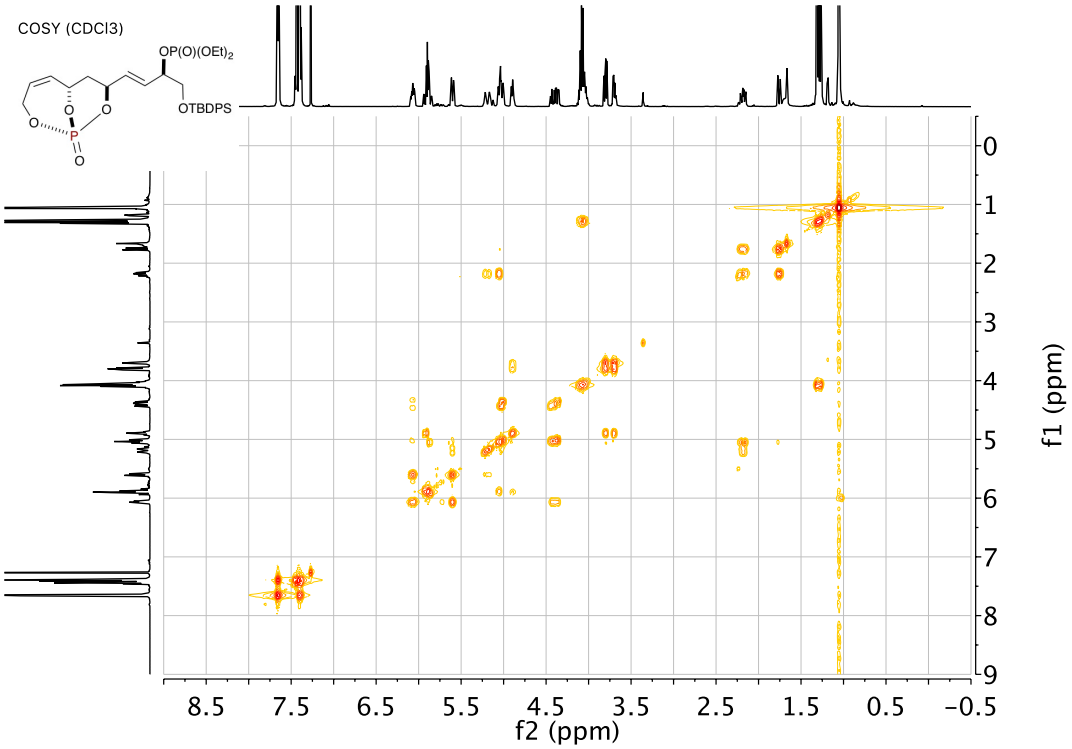
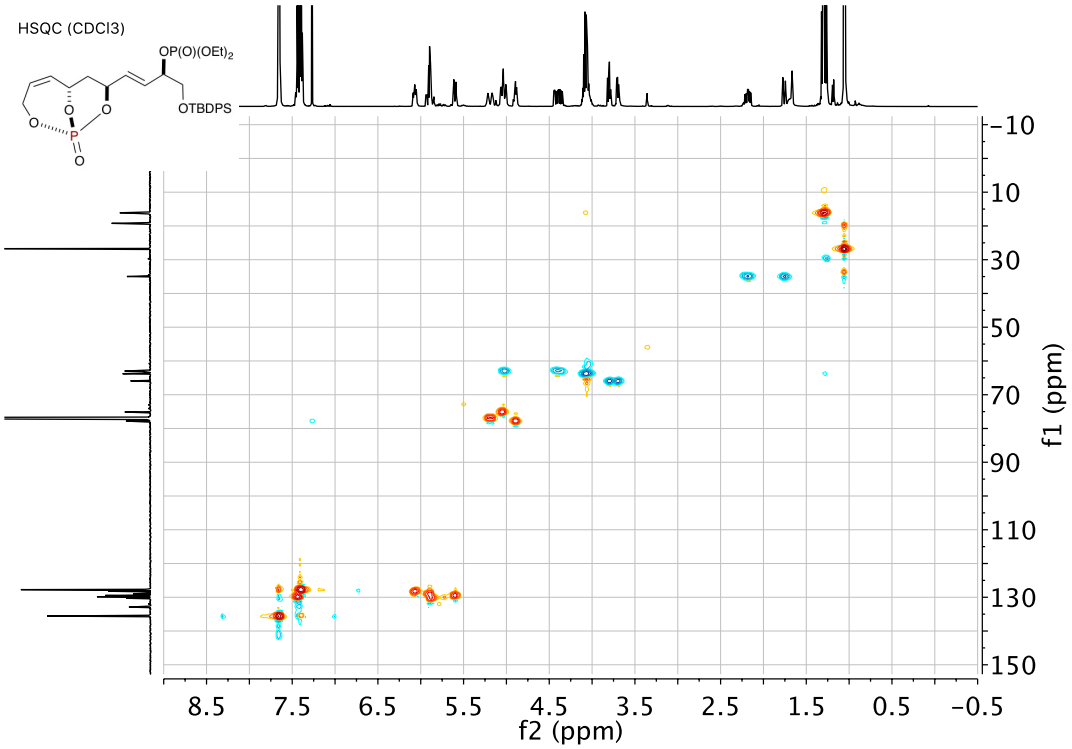
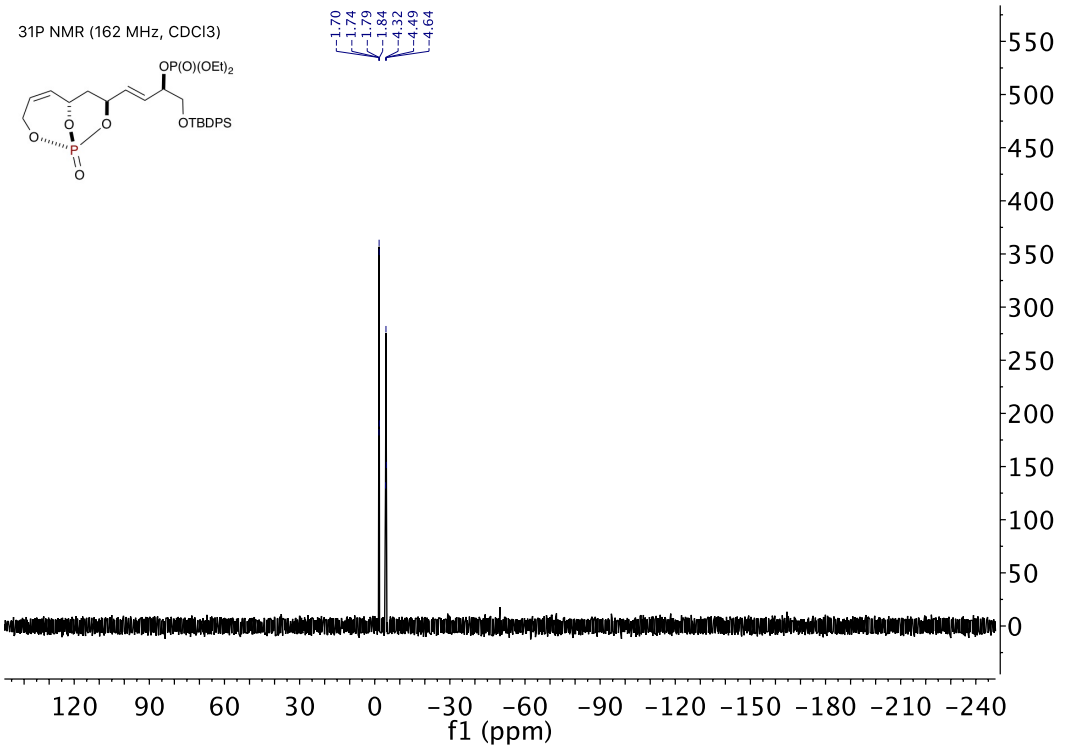
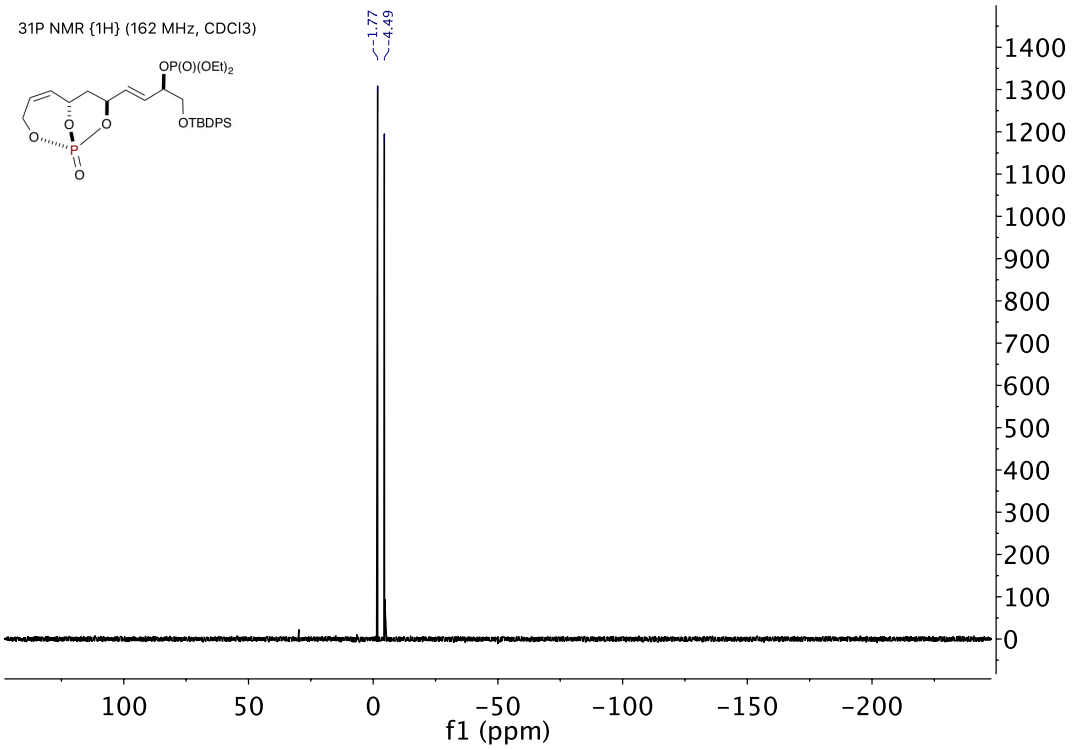
110
90
70
50
30
10
-10
f1 (ppm)

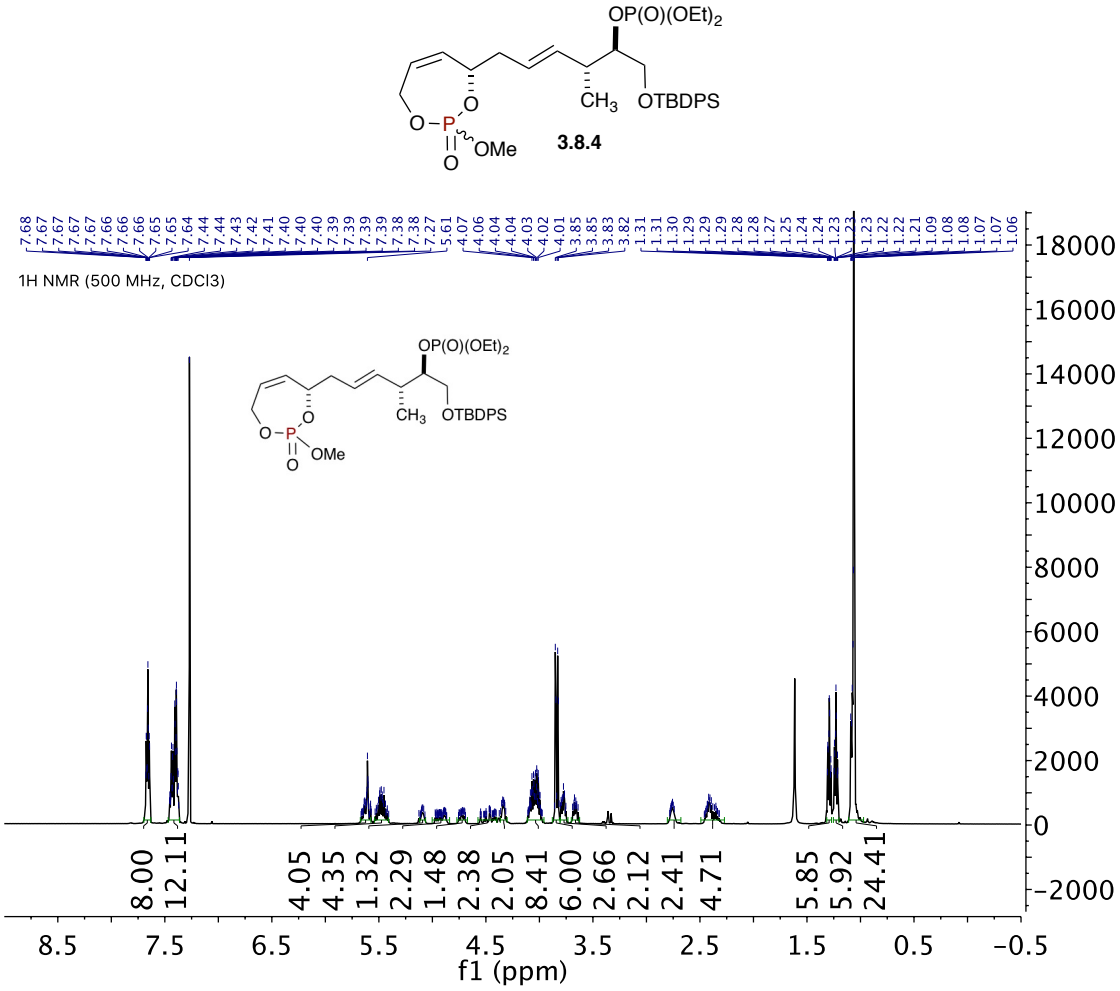

COSY (CDCl3)
OP(O)(OEt)2
OTBDPS
f2 (ppm)
f1 (ppm)

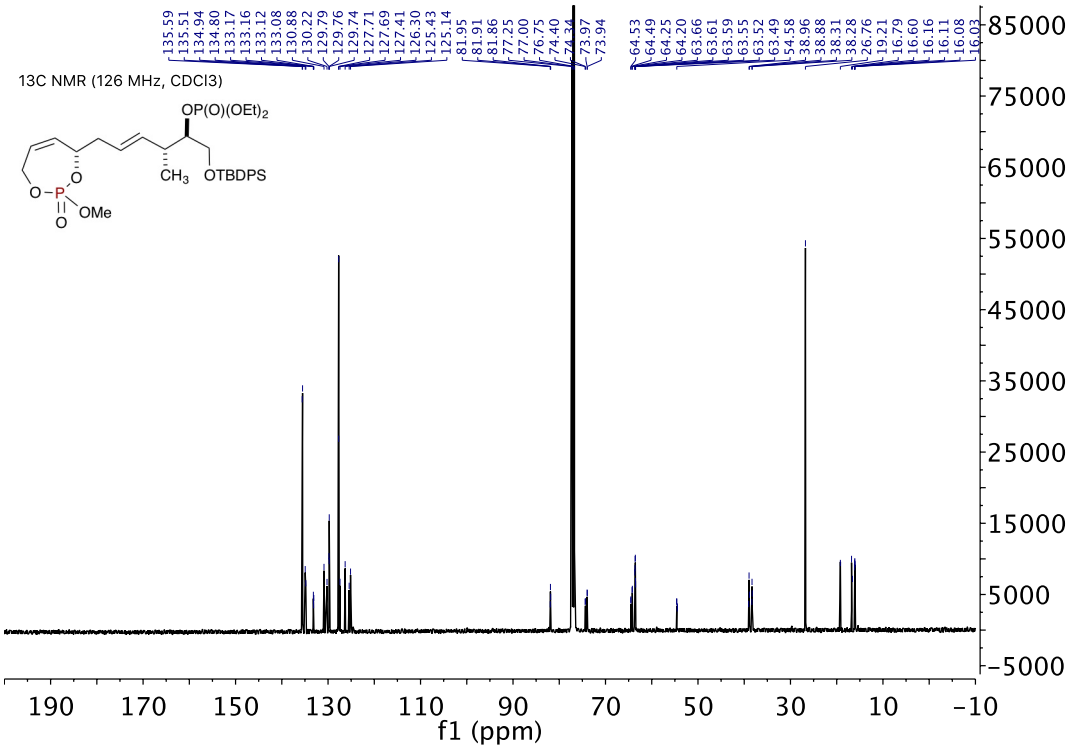

HSQC (CDCl3)
OP(O)(OEt)2
OTBDPS
f2 (ppm)
f1 (ppm)

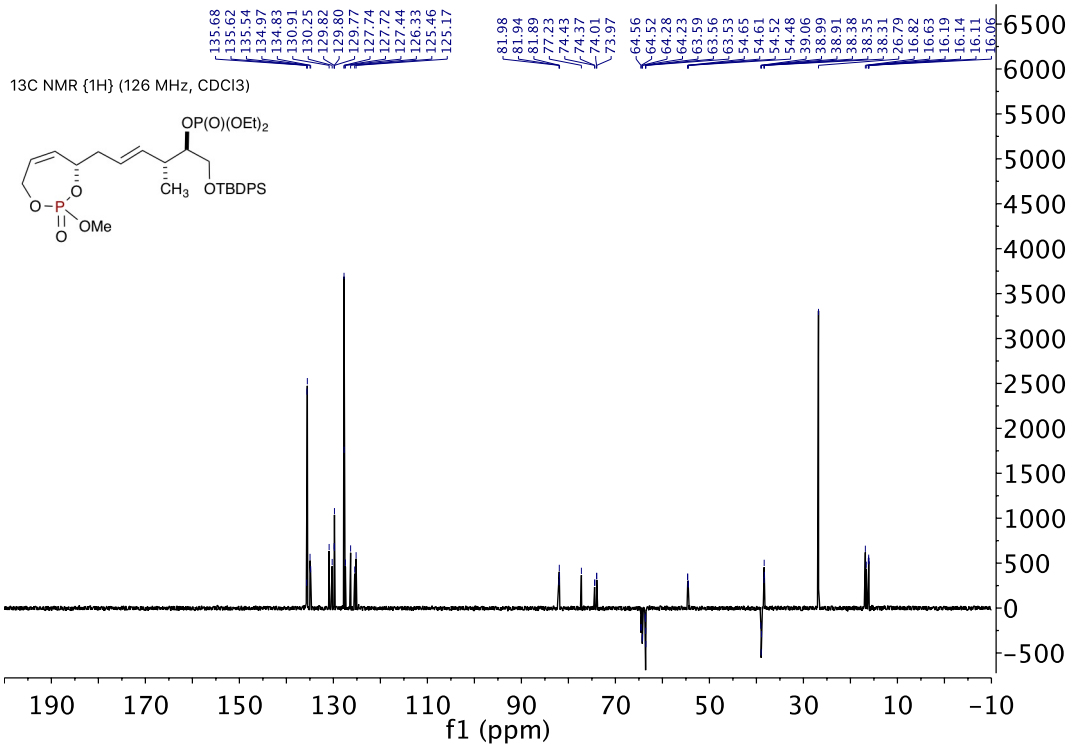

31P NMR (162 MHz, CDCl3)
OP(O)(OEt)2
OTBDPS
1.70
1.74
1.79
1.84
4.32
4.49
4.64
550
500
450
400
350
300
250
200
150
100
50
0
120 90 60 30 0 -30 -60 -90 -120 -150 -180 -210 -240
f1 (ppm)

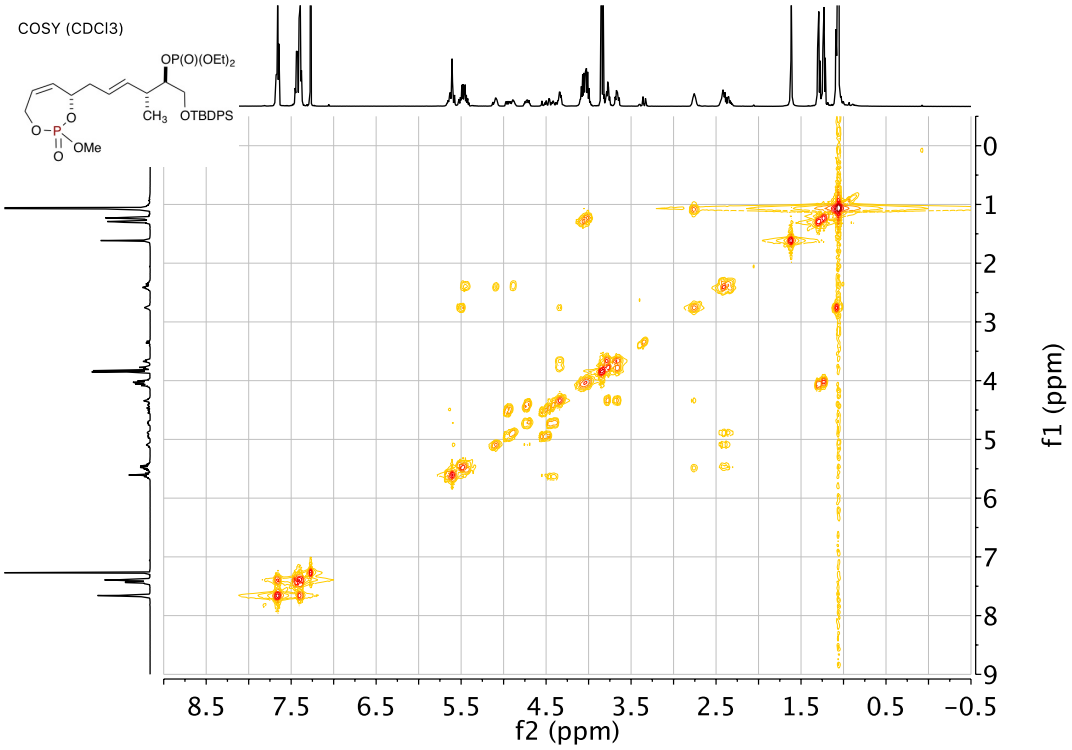

31P NMR {1H} (162 MHz, CDCl3)
OP(O)(OEt)2
OTBDPS
1.77
4.49
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
100 50 0 -50 -100 -150 -200
f1 (ppm)

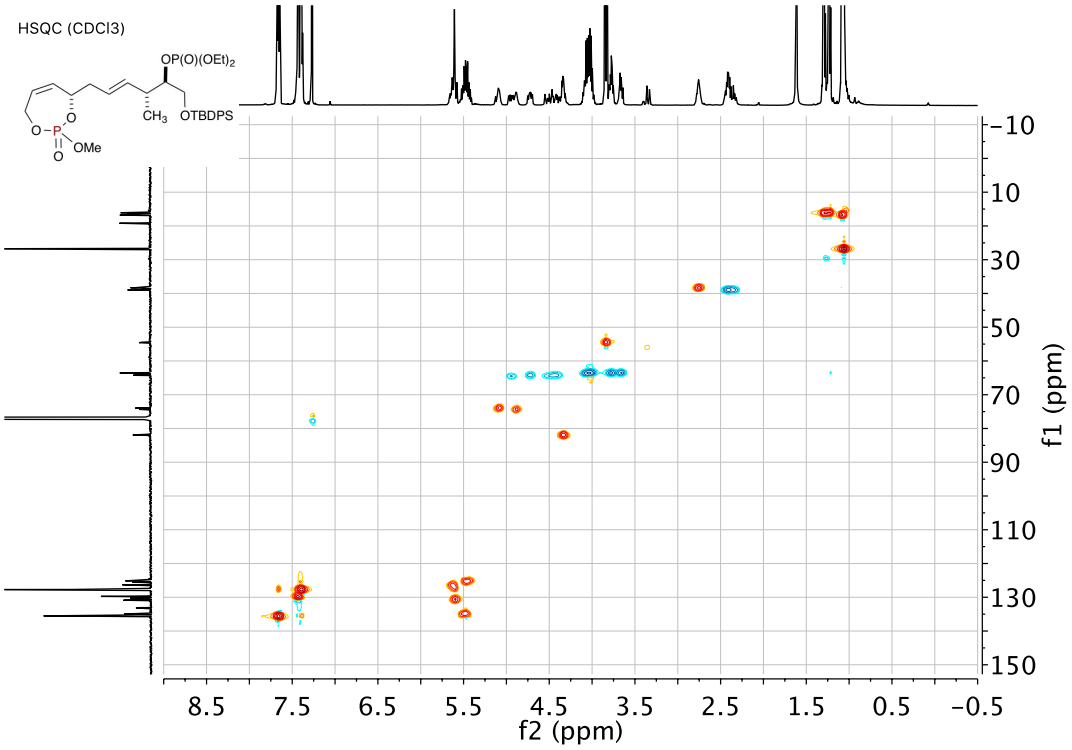
**(2*R*,3*R*,*E*)-1-((*tert*-butyldiphenylsilyl)oxy)-6-((4*S*)-2-methoxy-2-oxido-4,7-dihydro-1,3,2-dioxaphosphepin-4-yl)-3-methylhex-4-en-2-yl diethyl phosphate ($C_{32}H_{48}O_9P_2Si$, 3.8.4)**

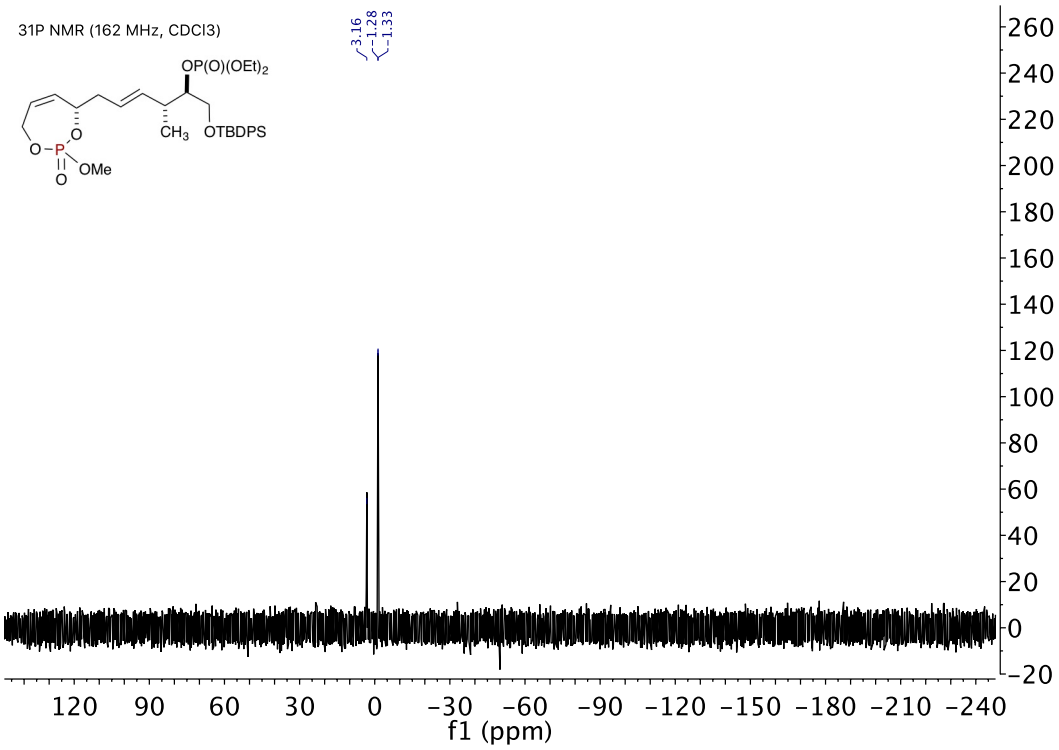


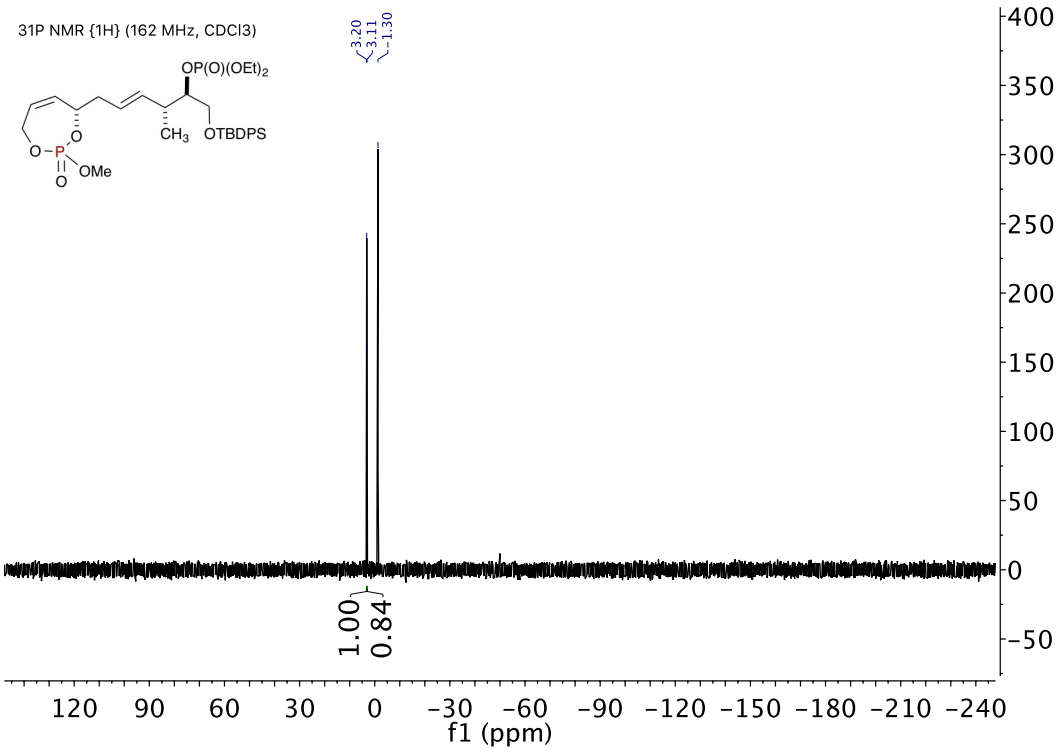

13C NMR (126 MHz, CDCl3)
OP(O)(OEt)2
CH3
OTBDPS
OMe
f1 (ppm)


13C NMR {1H} (126 MHz, CDCl3)
OP(O)(OEt)2
CH3
OTBDPS
OMe
f1 (ppm)


COSY (CDCl3)
OP(O)(OEt)2
CH3
OTBDPS
O
P
OMe
O
0
1
2
3
4
5
6
7
8
9
f1 (ppm)
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f2 (ppm)


HSQC (CDCl3)
OP(O)(OEt)2
CH3
OTBDPS
O
P
OMe
O
-10
10
30
50
70
90
110
130
150
f1 (ppm)
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f2 (ppm)


31P NMR (162 MHz, CDCl3)
3.16
1.28
1.33
OP(O)(OEt)2
CH3
OTBDPS
O
P
OMe
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
120 90 60 30 0 -30 -60 -90 -120 -150 -180 -210 -240
f1 (ppm)


31P NMR {1H} (162 MHz, CDCl3)
3.20
3.11
1.30
OP(O)(OEt)2
CH3
OTBDPS
O
P
OMe
400
350
300
250
200
150
100
50
0
-50
1.00
0.84
120 90 60 30 0 -30 -60 -90 -120 -150 -180 -210 -240
f1 (ppm)

## 5.3 Supporting Information for Chapter 4

*Phosphate Tether Methods Toward the*

*Modular Total Synthesis of 2*S*-Sanctolide A*

# *Table of Contents*

## Chapter 5, Section 3: Supporting Information for Chapter 4

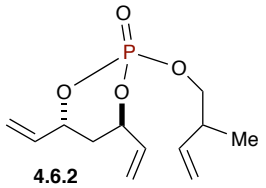
*Phosphate Tether Methods Toward the Modular Total Synthesis of 2*S*-Sanctolide A*

### 5.3.1 General Methods

All reactions were carried out in oven- or flame-dried glassware under argon atmosphere using standard gas-tight syringes, cannulae, and septa. Stirring was achieved with oven-dried magnetic stir bars. $Et_2O$, THF and $CH_2Cl_2$ were purified by passage through a purification system (Solv-Tek) employing activated $Al_2O_3$ (Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520). $Et_3N$ was purified by passage over basic alumina and stored over KOH. Butyllithium was purchased from Aldrich and titrated prior to use. All olefin metathesis catalysts were acquired from Materia and used without further purification. Flash column chromatography was performed with Sorbent Technologies (30930M-25, Silica Gel 60A, 40-63 mm) and thin layer chromatography was performed on silica gel $60F_{254}$ plates (EM-5717, Merck). Deuterated solvents were purchased from Cambridge Isotope laboratories. $^{1}H$, $^{13}C$, and corresponding 2D NMR spectra were recorded in $CDCl_3$ (unless otherwise mentioned) on a Bruker DRX-500 spectrometer operating at 500 MHz, and 125 MHz, respectively and calibrated to the solvent peak. $^{31}P$ and $^{1}H$-decoupled $^{31}P$ NMR spectra were recorded on a Bruker DRX-400 spectrometer operating at 162 MHz. High-resolution mass spectrometry (HRMS) was recorded on a LCT Premier Spectrometer (Micromass UK Limited) operating on ESI-positive mode (MeOH). Observed rotations at 589 nm, were measured using AUTOPOL IV Model automatic polarimeter. IR was recorded on Shimadzu FTIR-8400S instrument.

### 5.3.2 Experimental Section

**(4*R*,6*R*)-2-((2-methylbut-3-en-1-yl)oxy)-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide ($C_{12}H_{19}O_4P$, 4.6.2)**




**4.6.2**

To a solution of 2-methyl-3-buten-1-ol (1.35 g, 15.6 mmol) in THF (31 mL), under argon at -40 $^{o}$C, was added *n*-butyllithium (6.3 mL, 2.5 M in hexanes), dropwise. The reaction mixture stirred at -30 $^{o}$C for 15 minutes, at which point a solution of monochlorophosphate (*S*,*S*)-**2.2A**[1] (3.59 g, 17.2 mmol) in THF (34 mL) was added dropwise, slowly. The reaction continued to stir at -40 $^{o}$C for 30 minutes (complete by TLC), and the flask was removed from the cooling bath and quenched with saturated $NH_4Cl$ (aqueous, ~40 mL). The mixture was stirred, vigorously, as the flask warmed to room temperature, and then the biphasic solution was separated. The aqueous layer was extracted with EtOAc (3 x 50 mL), and the organic layers were combined, washed with brine, dried over $Na_2SO_4$, and concentrated under reduced pressure. The crude mixture was purified via flash column chromatography (silica, 0%–60% EtOAc in hexanes) to provide triene **4.6.2** (3.24 g, 12.5 mmol, 80% yield) as a colorless liquid and a 1:1 mixture of inseparable diastereomers.

---

[1]Whitehead, A.; McReynolds, M. D.; Moore, J. D.; Hanson, P. R. Multivalent Activation in Temporary Phosphate Tethers: A New Tether for Small Molecule Synthesis. *Org. Lett.* **2005**, *7*, 3375–3378.

**FTIR** (neat): 2966, 2934, 2895, 1423, 1283, 1119, 1013, 966, 928, 876, 756, 725 $cm^{-1}$;

**Optical Rotation**: $[\alpha]_D = -61.7$ ($c = 0.54$, $CHCl_3$);

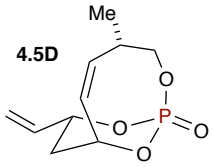
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.07 – 5.99 (m, 2H), 5.94 – 5.86 (m, 2H), 5.75 (dddd, $J$ = 17.4, 10.5, 7.0, 3.5 Hz, 2H), 5.46 (dt, $J$ = 17.1, 1.2 Hz, 2H), 5.37 (dt, $J$ = 17.2, 1.1 Hz, 2H), 5.31 (dt, $J$ = 3.5, 1.2 Hz, 2H), 5.29 (dt, $J$ = 3.5, 1.1 Hz, 2H), 5.14 – 5.08 (m, 2H), 5.09 – 5.00 (m, 4H), 4.97 (dtdt, $J$ = 8.5, 5.2, 3.4, 1.6 Hz, 2H), 4.03 – 3.91 (m, 4H), 2.63 – 2.49 (m, 2H), 2.17 (dddd, $J$ = 14.8, 8.3, 4.9, 1.5 Hz, 2H), 2.07 – 1.99 (m, 2H), 1.06 (dd, $J$ = 6.8, 0.7 Hz, 6H);

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 139.49 (d, $J_{CP}$ = 5.6 Hz, CH x 2), 135.1 (CH x 2), 135.0 (d, $J_{CP}$ = 4.0 Hz, CH x 2), 118.13 ($CH_2$), 118.11 ($CH_2$), 117.46 ($CH_2$), 117.45 ($CH_2$), 115.53 ($CH_2$), 115.47 ($CH_2$), 77.9 (d, $J_{CP}$ = 6.8 Hz, CH x 2), 76.04 (d, $J_{CP}$ = 5.8 Hz, CH), 76.01 (d, $J_{CP}$ = 6.0 Hz, CH), 71.6 (d, $J_{CP}$ = 6.3 Hz, $CH_2$ x 2), 38.3 (d, $J_{CP}$ = 7.3 Hz, CH), 38.2 (d, $J_{CP}$ = 6.9 Hz, CH), 35.21 (d, $J_{CP}$ = 7.6 Hz, $CH_2$), 35.17 (d, $J_{CP}$ = 7.9 Hz, $CH_2$), 16.1 ($CH_3$), 16.0 ($CH_3$);

**$^{31}$P NMR** (162 MHz, $CDCl_3$) δ –7.66 (dp, $J$ = 13.3, 6.6 Hz);

**HRMS** cald for $C_{12}H_{19}O_4PNa$ $(M+Na)^+$ 281.0919; found 281.0912 (TOF MS ES+).

**(1*R*,4*S*,7*R*,9*R*,*Z*)-4-methyl-9-vinyl-2,10,11-trioxa-1-phosphabicyclo[5.3.1]undec-5-ene 1-oxide ($C_{10}H_{15}O_4P$, 4.5D)**




To a round bottom flask, equipped with a stirbar, reflux condenser, and argon inlet, was added triene **4.6.2** (2.50 g, 9.68 mmol), $CH_2Cl_2$ (1383 mL), and Grubbs second-generation catalyst [$(ImesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$,[2] G-II, 123 mg, 1.5 mol %]. The reaction mixture was heated to reflux and stirred at reflux for 2 hours to ensure complete conversion of reactive starting material (~1:1 mix of starting material and product by TLC). The reaction mix was cooled to room temperature and concentrated under reduced pressure. Purification via flash column chromatography (silica, 0%–70% EtOAc in hexanes) provided bicyclic phosphate **4.5D** (0.850 g, 3.69 mmol, 38% yield) as a white solid, along with unreacted starting material (0.800 g, 3.098 mmol).

**FTIR** (neat): 2964, 2932, 2893, 1464, 1429, 1286, 1130, 1080, 1059, 1020, 966, 932, 850, 837, 820, 735, 500 $cm^{-1}$;

**Optical Rotation**: $[\alpha]_D = -138$. (*c* = 0.57, $CHCl_3$);

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 5.83 (dddd, *J* = 17.1, 10.6, 5.4, 2.1 Hz, 1H, -C<u>H</u>=$CH_2$), 5.46 – 5.43 (m, 2H, (P)O-CH-C<u>H</u>=C<u>H</u>-$CH(CH_3)$-), 5.40 (dt, *J* = 17.1, 1.2 Hz, 1H, -CH=C<u>H</u>$_a$H$_b$), 5.29 – 5.21 (m, 2H, -CH=CH$_a$<u>H</u>$_b$, (P)O-C<u>H</u>-CH=CH-$CH(CH_3)$-), 5.06 (ddt,

[2] Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. Synthesis and Activity of a New Generation of Ruthenium-Based Olefin Metathesis Catalysts Coordinated with 1,3-Dimesityl-4,5-dihydroimidazol-2-ylidene Ligands. *Org. Lett.* **1999**, *1*, 953–956.

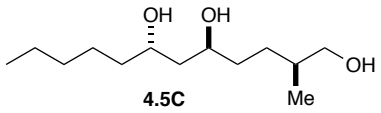
*J* = 11.9, 5.4, 1.5 Hz, 1H, (P)O-C<u>H</u>($CH_2$)-CH=$CH_2$), 4.30 (ddd, *J* = 10.8, 6.2, 2.1 Hz, 1H, -CH=CH-CH($CH_3$)-C<u>H</u>$_a$H$_b$-O(P)), 3.60 – 3.50 (m, 1H, (P)O-CH-CH=CH-C<u>H</u>($CH_3$)-), 3.32 (ddd, *J* = 31.0, 12.6, 10.8 Hz, 1H, -CH=CH-CH($CH_3$)-CH$_a$<u>H</u>$_b$-O(P)), 2.18 (dddd, *J* = 14.6, 11.9, 6.0, 0.8 Hz, 1H, (P)O-CH-C<u>H</u>$_a$H$_b$-CH-O(P)), 1.87 – 1.77 (m, 1H, (P)O-CH-CH$_a$<u>H</u>$_b$-CH-O(P)), 0.99 (d, *J* = 6.6 Hz, 3H, (P)O-CH-CH=CH-CH(C<u>H</u>$_3$)-);

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 135.0 (d, $J_{CP}$ = 10.0 Hz, CH), 134.0 (CH), 129.3 (CH), 117.2 ($CH_2$), 77.9 (d, $J_{CP}$ = 7.2 Hz, CH), 77.1 (d, $J_{CP}$ = 6.0 Hz, CH), 68.1 (d, $J_{CP}$ = 5.3 Hz, $CH_2$), 36.2 (d, $J_{CP}$ = 6.4 Hz, $CH_2$), 31.1 (CH), 16.5 ($CH_3$);

**$^{31}$P NMR** (162 MHz, $CDCl_3$) δ –8.02 (dd, *J* = 30.7, 24.8 Hz);

**HRMS** cald for $C_{20}H_{30}O_8P_2Na$ $(2M+Na)^+$ 483.1314; found 483.1333 (TOF MS ES+).

**(2*S*,5*S*,7*S*)-2-methyldodecane-1,5,7-triol ($C_{13}H_{28}O_3$, 3.9.4)**




**4.5C**

To a clean, dry round bottom flask equipped with a stirbar, reflux condenser, and argon inlet, was added **4.5D** (60.0 mg, 0.261 mmol), 1,2-dichloroethane (1,2-DCE, 2.6 mL), *cis*-4-octene (73.1 mg, 0.652 mmol), and Hoveyda-Grubbs second-generation catalyst (HG-II, 9.7 mg, 6 mol %). The reaction was heated to 40 $^oC$ and stirred at 40 $^oC$ until **4.5D** was consumed (2 h, monitored by TLC). The reaction was cooled to room temperature and cannulated into a Parr hydrogenation reaction vessel. The vessel was heated to 70 $^oC$, and $H_2$ pressure was applied (1000 psi). The reaction stirred at 70 $^oC$,

under $H_2$ pressure, for 16 h (complete by TLC), at which point the reaction was cooled to room temperature and solvent removed under reduced pressure. The crude oil was dried under high vacuum (~8 h) to ensure complete removal of 1,2-DCE. The crude mix was taken up in diethyl ether ($Et_2O$, 4.3 mL) and cooled to 0 $^oC$ under argon. Solid lithium aluminum hydride (29.7 mg, 0.782 mmol) was added in one portion, and the reaction flask was removed from the cooling bath and allowed to warm to room temperature. The mixture stirred at room temperature for 1 hour (complete by TLC), and the reactiom was cooled to 0 $^oC$ and quenched by sequential addition of $H_2O$ and 10% NaOH (w/v, aq) [30 μL $H_2O$, 30 μL NaOH sln, 90 μL of $H_2O$]. The reaction was allowed to warm to room temperature and stir at room temperature overnight (white solids formed). The crude mixture was filtered over celite (washed with $CH_2Cl_2$, EtOAc, and MeOH) and concentrated under reduced pressure. Purification via flash column chromatography (silica, 0%–100% EtOAc in hexanes) provided **4.5C** (34.8 mg, 0.150 mmol, 57% yield over 3 reactions in one pot, 83% average per reaction) as a white solid.

**FTIR** (neat): 3333 (br), 2930, 2872, 1462, 1454, 1121, 1034, 829 $cm^{-1}$;

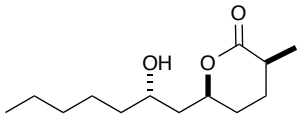
**Optical Rotation**: $[\alpha]_D = –2.5$ (*c* = 0.28, $CHCl_3$);

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 4.01 – 3.85 (m, 2H), 3.59 – 3.40 (m, 2H), 3.08 (s, 1H), 2.72 (s, 1H), 2.13 (s, 1H), 1.74 – 1.39 (m, 9H), 1.38 – 1.22 (m, 6H), 0.95 – 0.83 (m, 6H);

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 69.5 (CH), 69.2 (CH), 67.9 ($CH_2$), 42.5 ($CH_2$), 37.4 ($CH_2$), 35.3 (CH), 34.3 ($CH_2$), 31.8 ($CH_2$), 29.0 ($CH_2$), 25.5 ($CH_2$), 22.6 ($CH_2$), 16.6 ($CH_3$), 14.0 ($CH_3$);

**HRMS** cald for $C_{13}H_{28}O_3Na$ $(M+Na)^+$ 255.1936; found 255.1932 (TOF MS ES+).

**(3*S*,6*S*)-6-((*S*)-2-hydroxyheptyl)-3-methyltetrahydro-2*H*-pyran-2-one ($C_{13}H_{24}O_3$, 4.8.1)**




**4.8.1**

To a round bottom flask, equipped with a stirbar, was added **4.5C** (5.0 mg, 0.022 mmol), $CH_2Cl_2$ (0.4 mL), TEMPO (0.3 mg, 0.0022 mmol, 10 mol%), tetrabutylammonium chloride (TBACl, 0.6 mg, 0.0022 mmol, 10 mol%), and aqueous $NaHCO_3/K_2CO_3$ buffer (0.4 mL, 0.5 M $NaHCO_3$: 0.05 M $K_2CO_3$). To the stirring biphasic solution was added *N*-chlorosuccinimide (14.4 mg, 0.1075 mmol, 5 equiv.) in one portion, and the reaction continued to vigorously stir at room temperature for 2 hours (complete by TLC). The biphasic solution was diluted with $CH_2Cl_2$ (0.5 mL) and water (0.5 mL), and the layers separated. The aqueous layer was extracted with $CH_2Cl_2$ (3 x 1.5 mL), and the organic layers were combined, dried over $Na_2SO_4$, filtered over celite, and concentrated under reduced pressure. Purification via flash column chromatography (silica, 0%-50% EtOAc in hexanes) provided **4.8.1** (4.7 mg, 0.021 mmol, 96% yield) as a colorless liquid.

**FTIR** (neat): 3435 (br), 2953, 2930, 2858, 1738, 1726, 1462, 1454, 1379, 1227, 1200, 1117, 1082, 1024, 935 $cm^{-1}$;

**Optical Rotation**: $[\alpha]_D$ = +92.6 (*c* = 0.19 , $CHCl_3$);

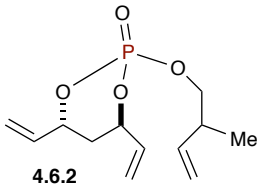
**$^{1}$H NMR** (500 MHz, $CDCl_3$) δ 4.64 (tt, *J* = 11.3, 3.0 Hz, 1H), 3.97 (t, *J* = 8.3 Hz, 1H), 2.64 (ddq, *J* = 10.6, 8.2, 6.8 Hz, 1H), 2.12 (dddd, *J* = 13.6, 9.6, 8.1, 7.2 Hz, 1H), 1.92 (dddd, *J* = 13.9, 9.4, 4.3, 3.4 Hz, 1H), 1.77 (ddd, *J* = 14.6, 9.8, 2.3 Hz, 1H), 1.67 (dddd, *J* = 14.0, 7.0, 4.1, 2.4 Hz, 2H), 1.61 – 1.54 (m, 2H), 1.49 – 1.39 (m, 3H), 1.30 (tdd, *J* = 15.0, 13.8, 6.9, 4.5 Hz, 5H), 1.23 (d, *J* = 6.7 Hz, 3H), 0.93 – 0.86 (m, 3H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 176.5 (C=O), 74.8 (CH), 67.6 (CH), 42.8 ($CH_2$), 38.1 ($CH_2$), 33.2 (CH), 31.8 ($CH_2$), 27.2 ($CH_2$), 25.7 ($CH_2$), 25.2 ($CH_2$), 22.6 ($CH_2$), 16.1 ($CH_3$), 14.0 ($CH_3$);

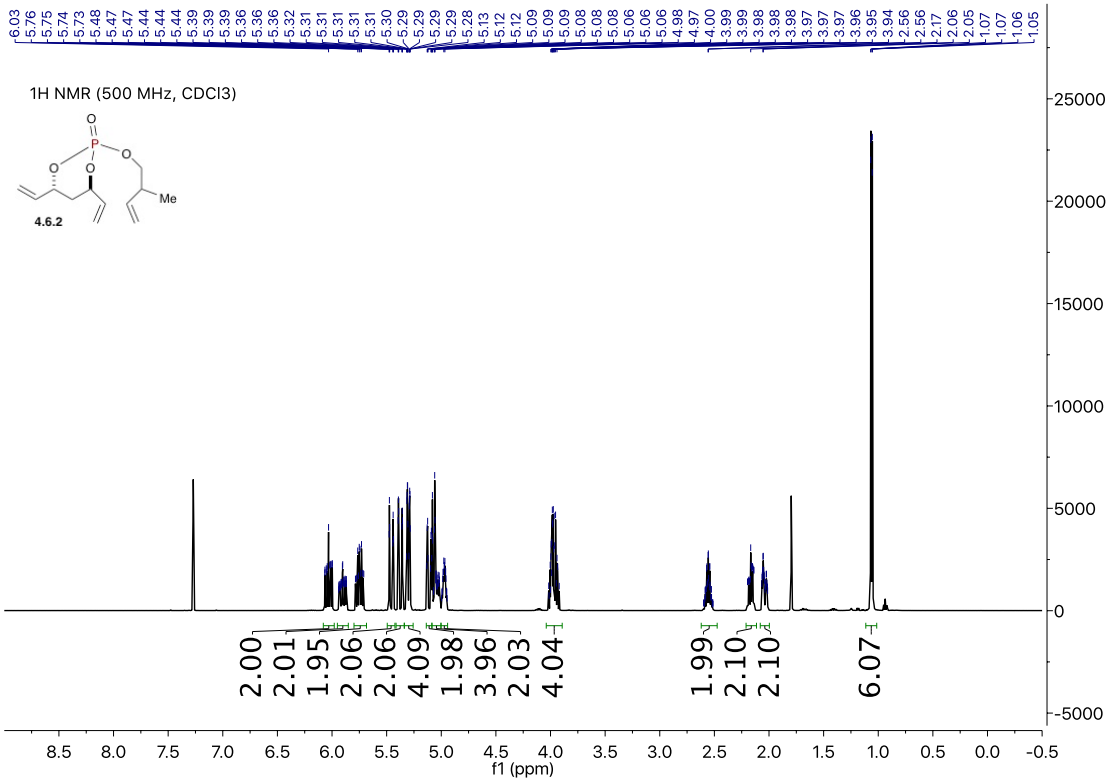
**HRMS** cald for $C_{13}H_{24}O_3Na$ $(M+Na)^+$ 251.1623; found 251.1612 (TOF MS ES+).

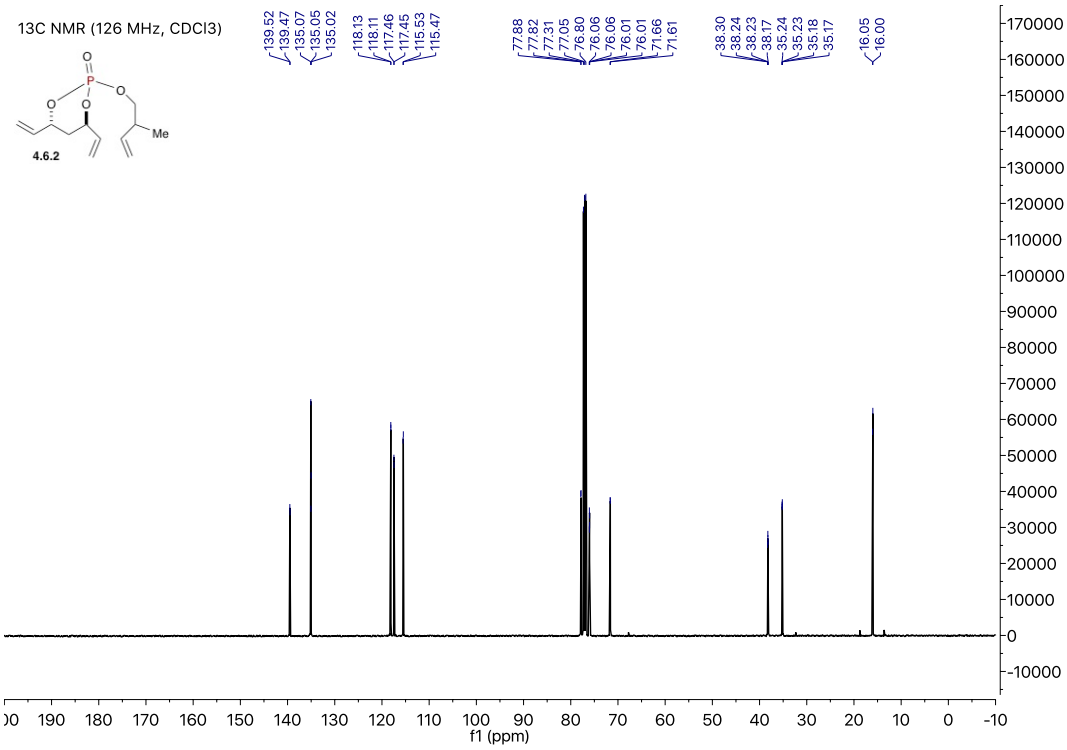
### 5.3.3 NMR Spectra

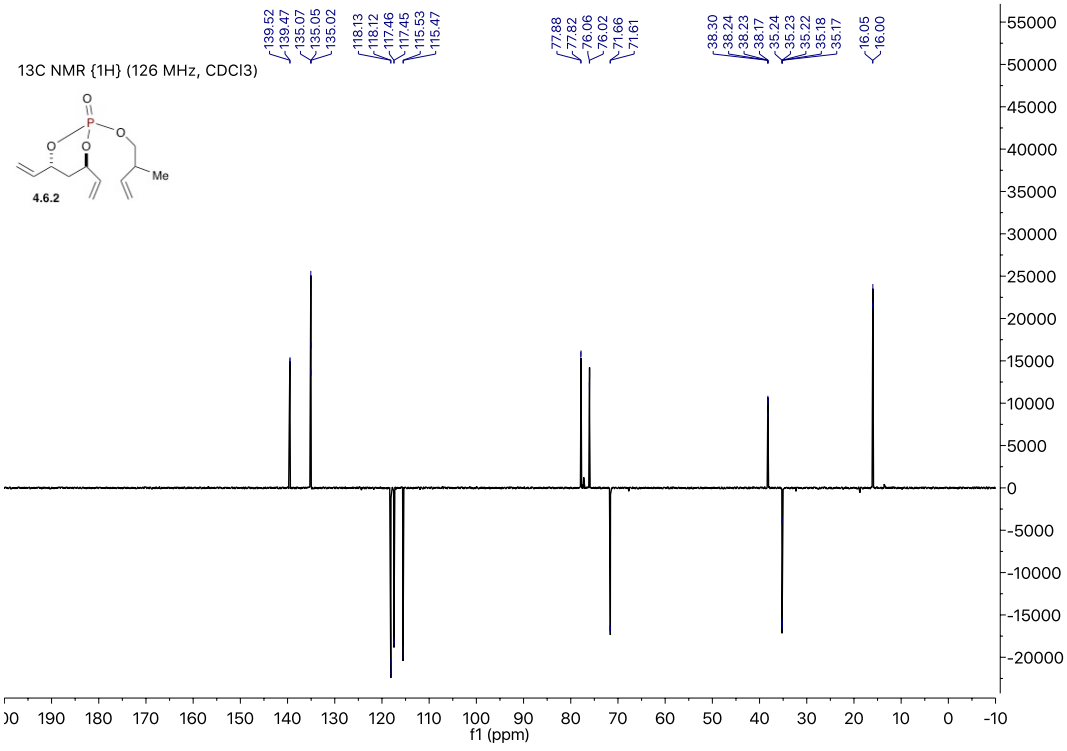
**(4*R*,6*R*)-2-((2-methylbut-3-en-1-yl)oxy)-4,6-divinyl-1,3,2-dioxaphosphinane 2-oxide ($C_{12}H_{19}O_4P$, 4.6.2)**

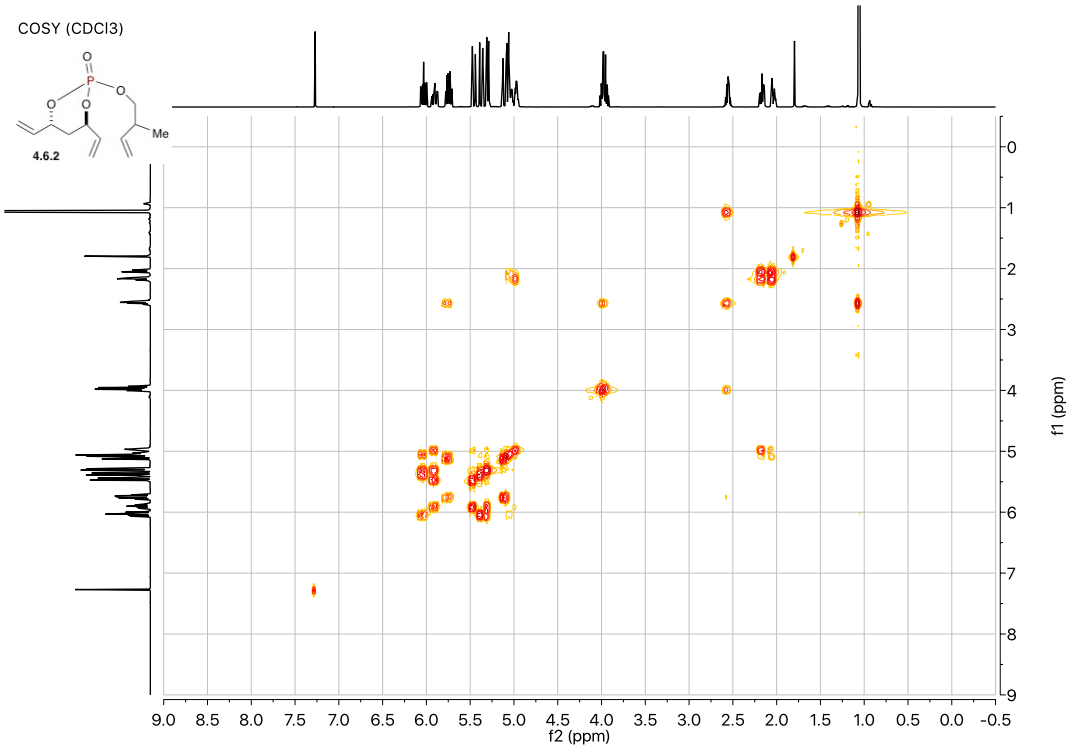


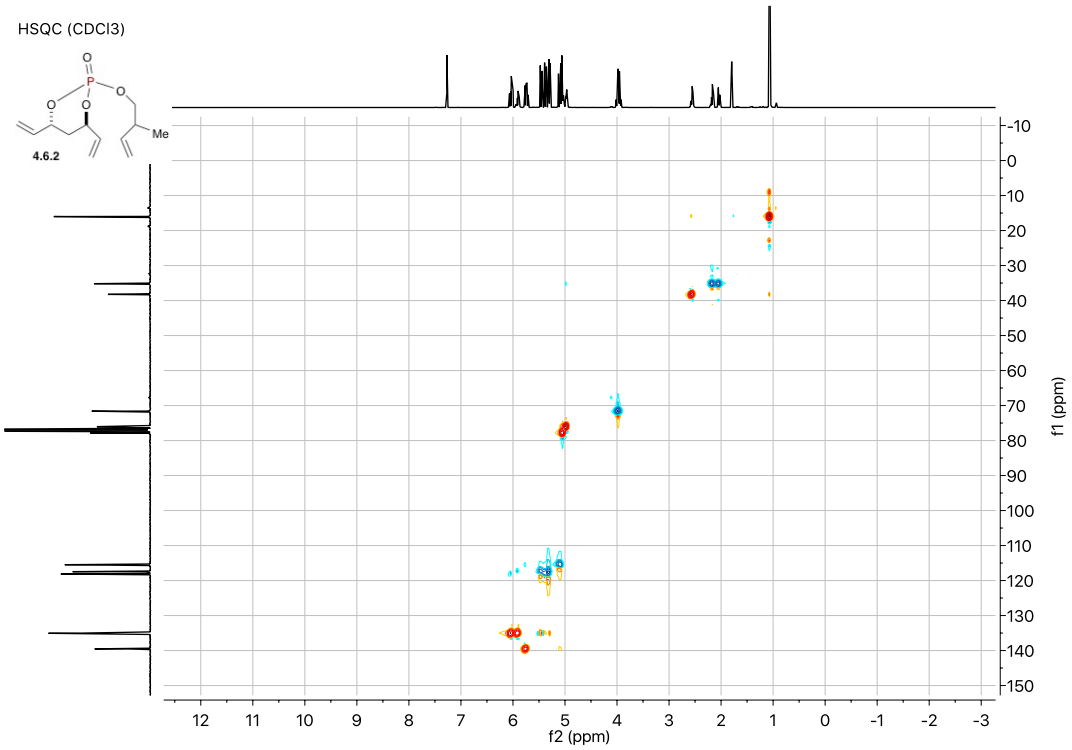

4.6.2

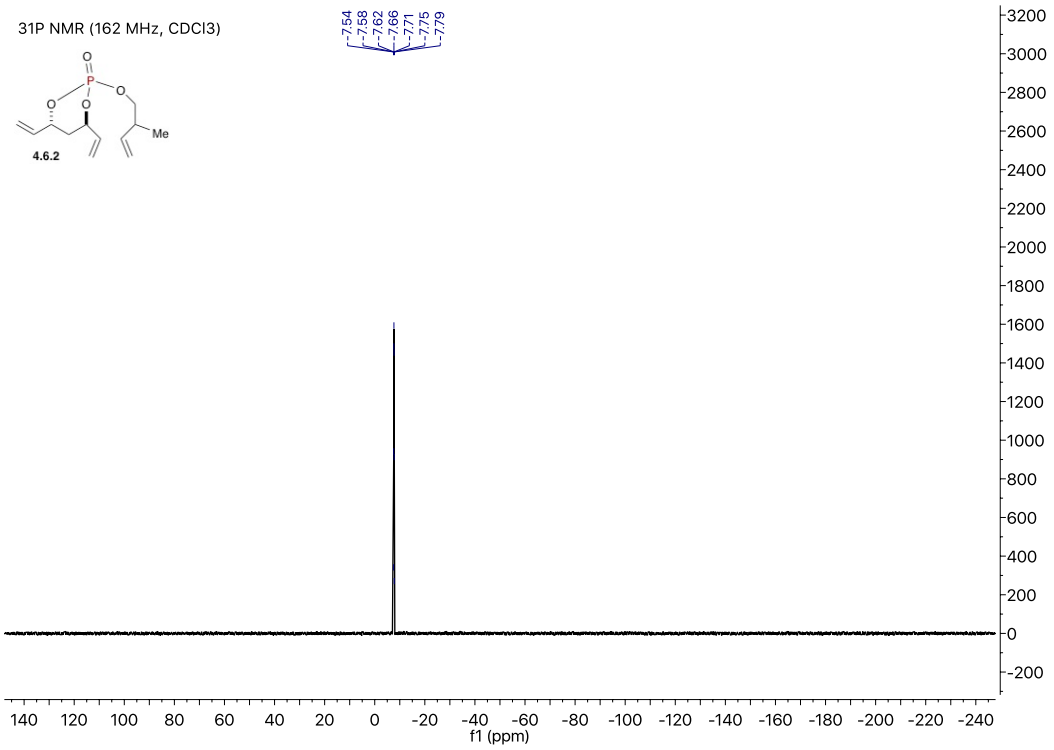


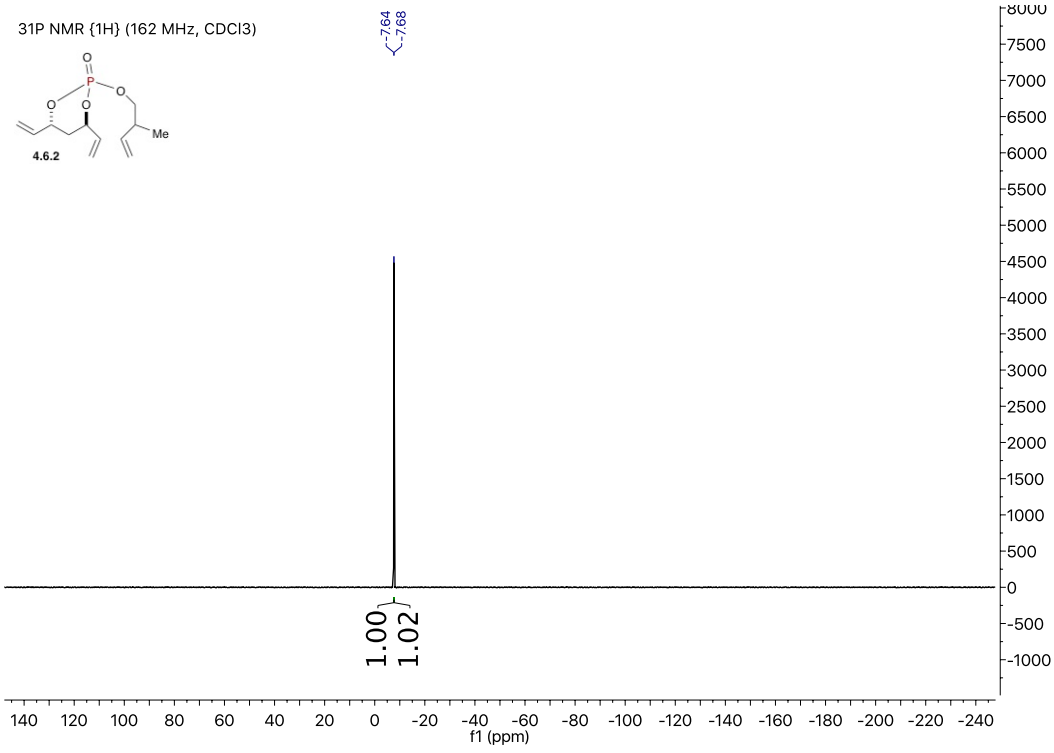

13C NMR (126 MHz, CDCl3)
4.6.2
Me
139.52
139.47
135.07
135.05
135.02
118.13
118.11
117.46
117.45
115.53
115.47
77.88
77.82
77.31
77.05
76.80
76.06
76.06
76.01
76.01
71.66
71.61
38.30
38.24
38.23
38.17
35.24
35.23
35.18
35.17
16.05
16.00
f1 (ppm)


13C NMR {1H} (126 MHz, CDCl3)
4.6.2
Me
139.52
139.47
135.07
135.05
135.02
118.13
118.12
117.46
117.45
115.53
115.47
77.88
77.82
76.06
76.02
71.66
71.61
38.30
38.24
38.23
38.17
35.24
35.23
35.22
35.18
35.17
16.05
16.00
f1 (ppm)

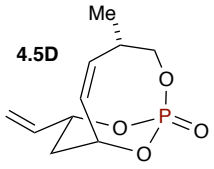

COSY (CDCl3)
4.6.2
Me
f2 (ppm)
f1 (ppm)

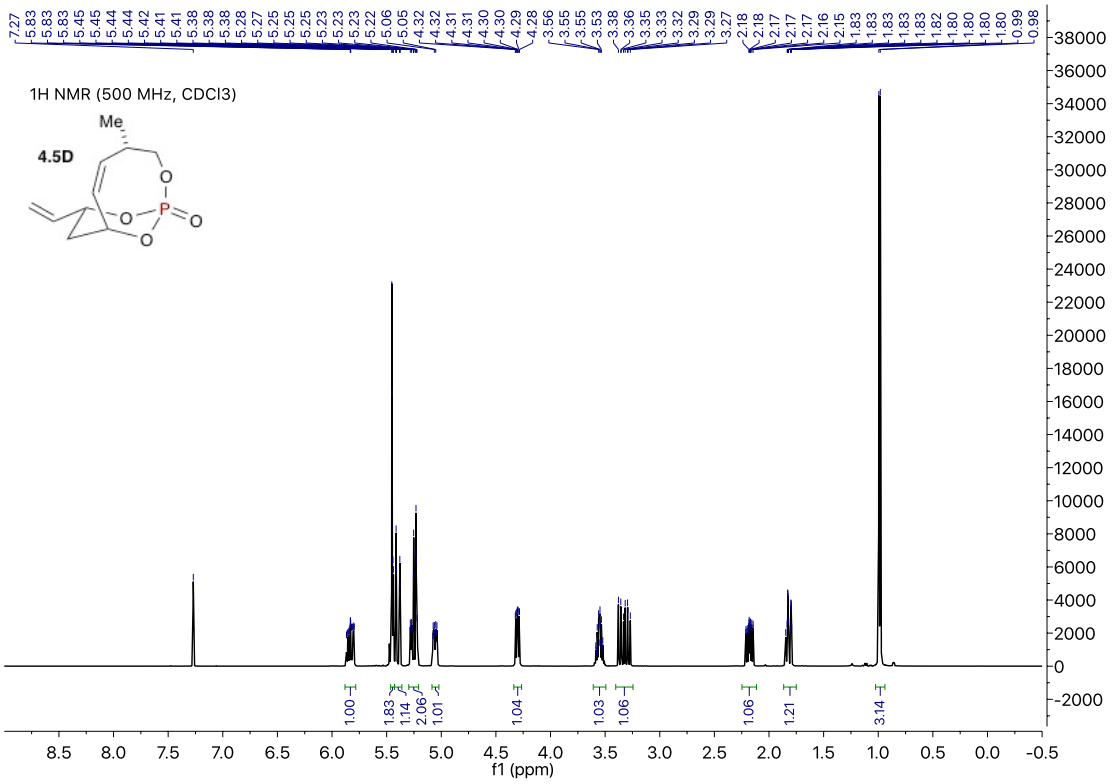

HSQC (CDCl3)
4.6.2
Me
f2 (ppm)
f1 (ppm)

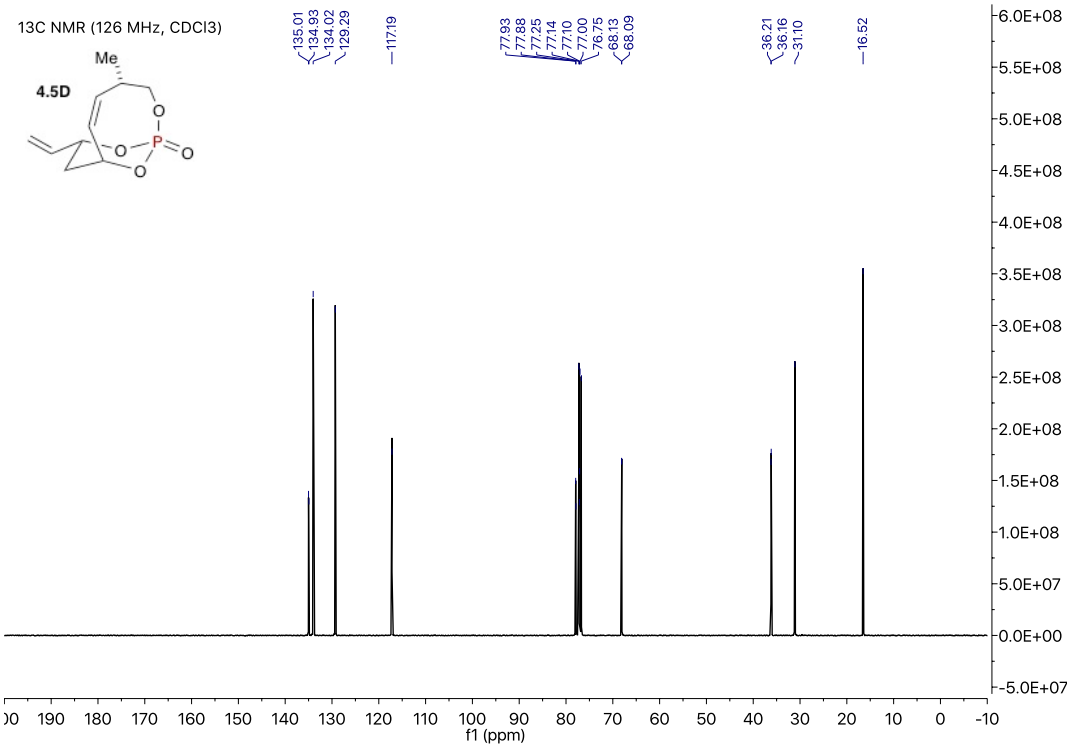

31P NMR (162 MHz, CDCl3)
7.54
7.58
7.62
7.66
7.71
7.75
7.79
4.6.2
Me
f1 (ppm)

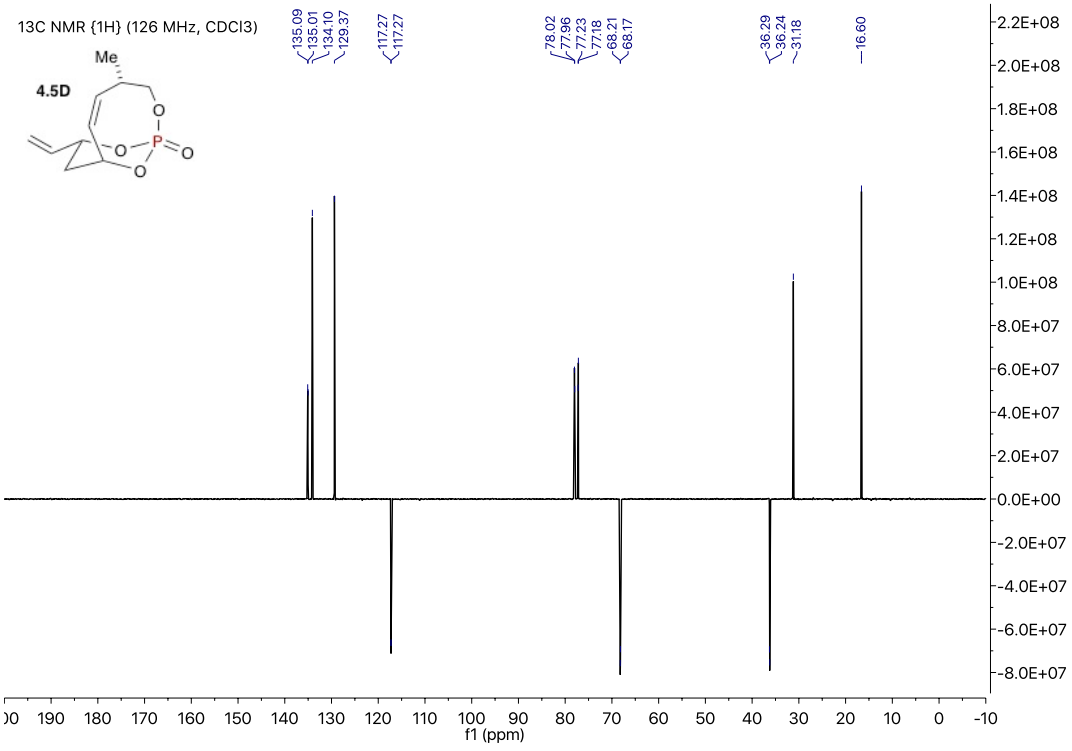

31P NMR {1H} (162 MHz, CDCl3)
7.64
7.68
4.6.2
Me
1.00
1.02
f1 (ppm)

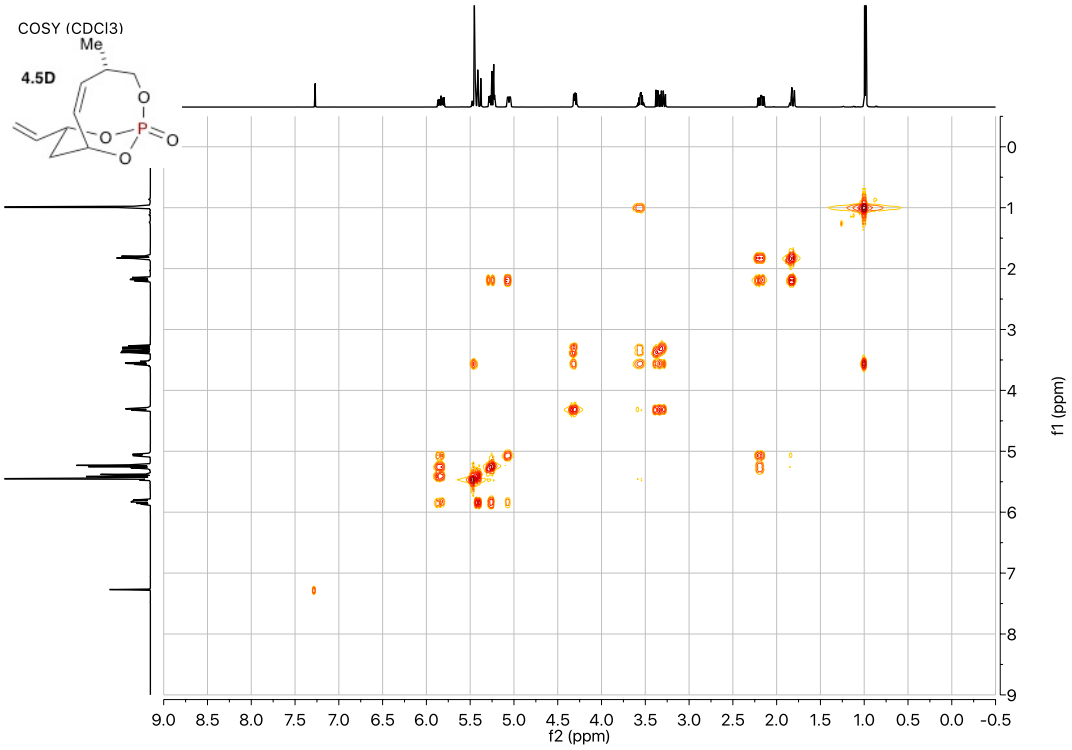
**(1*R*,4*S*,7*R*,9*R*,*Z*)-4-methyl-9-vinyl-2,10,11-trioxa-1-phosphabicyclo[5.3.1]undec-5-ene 1-oxide ($C_{10}H_{15}O_4P$, 4.5D)**

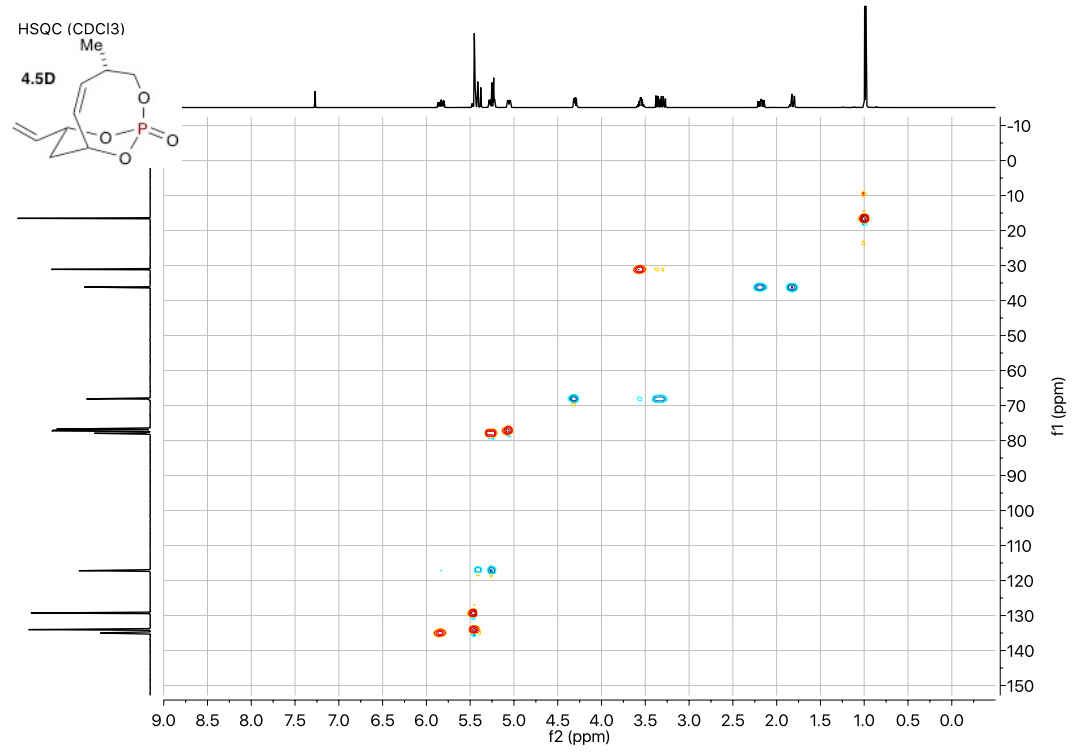


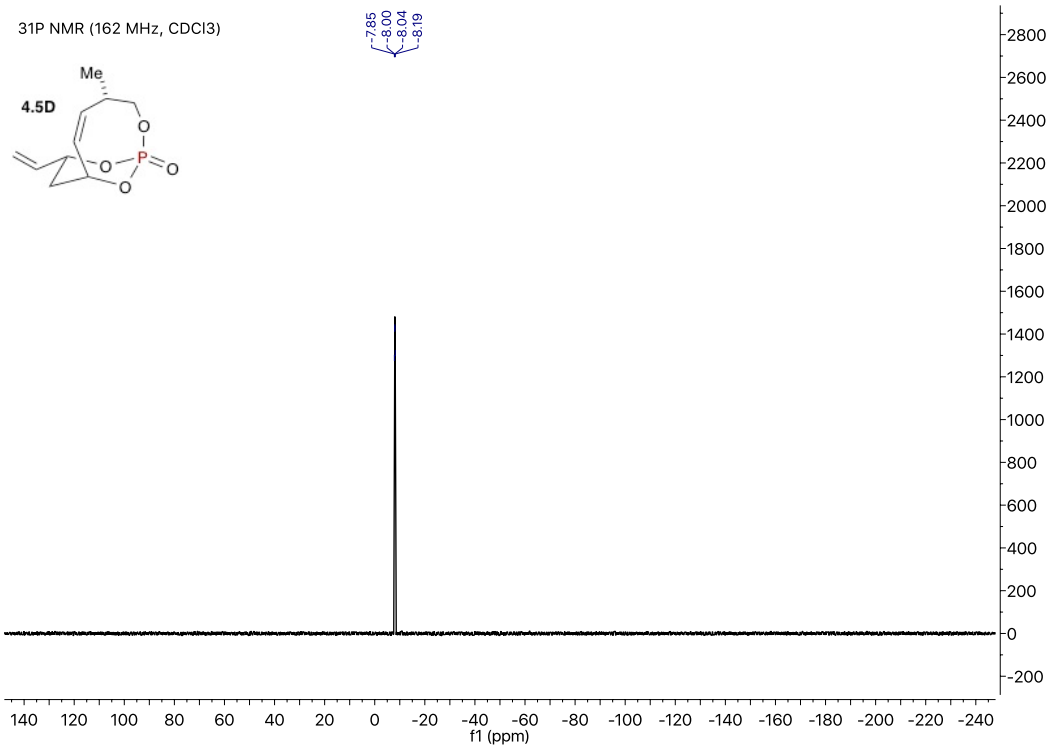



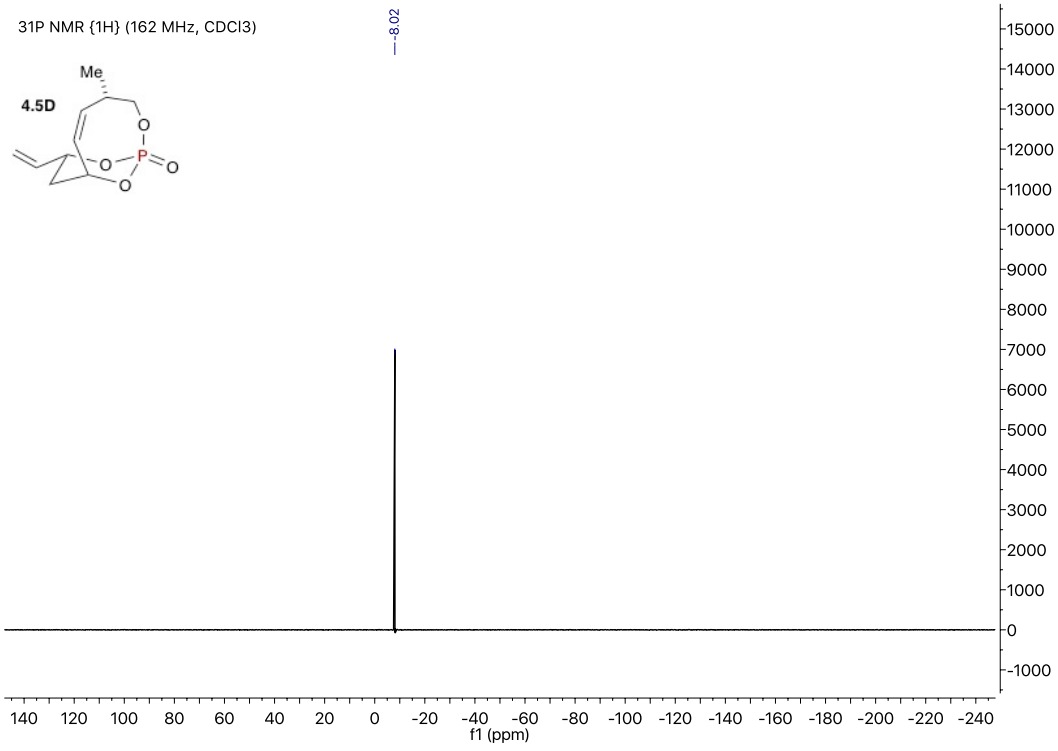

13C NMR (126 MHz, CDCl3)
Me
4.5D
135.01
134.93
134.02
129.29
117.19
77.93
77.88
77.25
77.14
77.10
77.00
76.75
68.13
68.09
36.21
36.16
31.10
16.52
f1 (ppm)


13C NMR {1H} (126 MHz, CDCl3)
Me
4.5D
135.09
135.01
134.10
129.37
117.27
117.27
78.02
77.96
77.23
77.18
68.21
68.17
36.29
36.24
31.18
16.60
f1 (ppm)

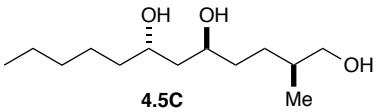

COSY (CDCl3)
Me
4.5D
O
O
P
O
O
O
f2 (ppm)
f1 (ppm)


HSQC (CDCl3)
Me
4.5D
O
O
P
O
O
O
f2 (ppm)
f1 (ppm)

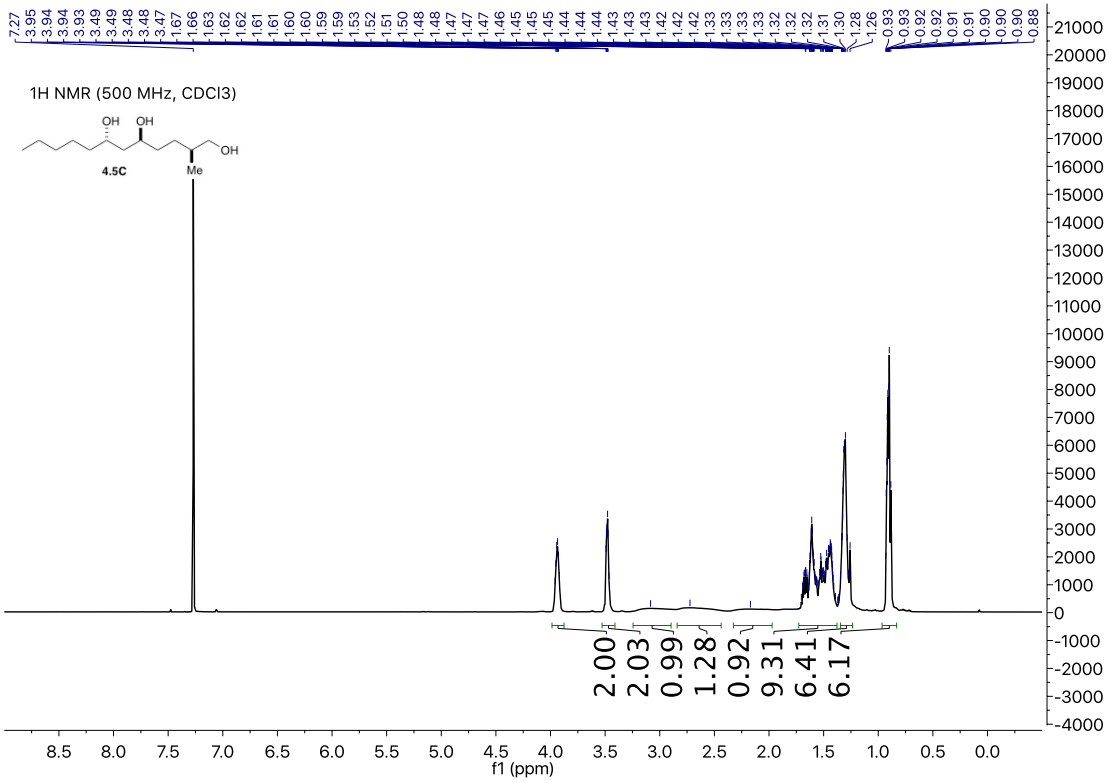

31P NMR (162 MHz, CDCl3)
7.85
8.00
8.04
8.19
Me
4.5D
O
O
P
O
O
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
140 120 100 80 60 40 20 0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 -220 -240
f1 (ppm)

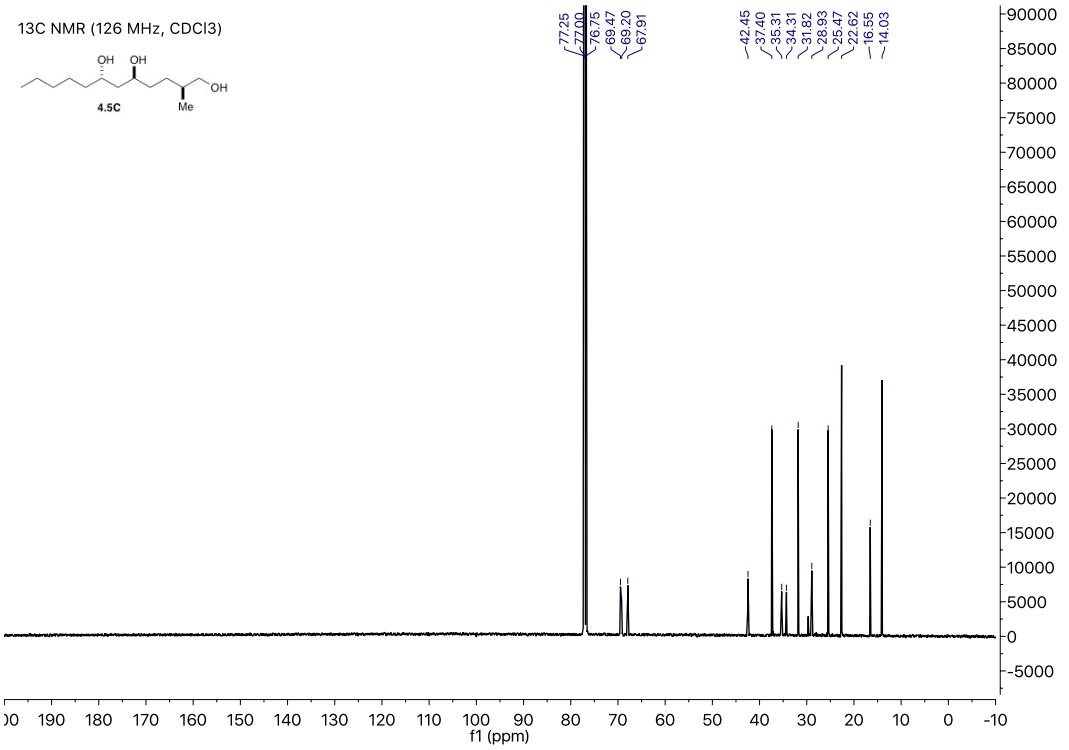

31P NMR {1H} (162 MHz, CDCl3)
8.02
Me
4.5D
O
O
P
O
O
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
140 120 100 80 60 40 20 0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 -220 -240
f1 (ppm)

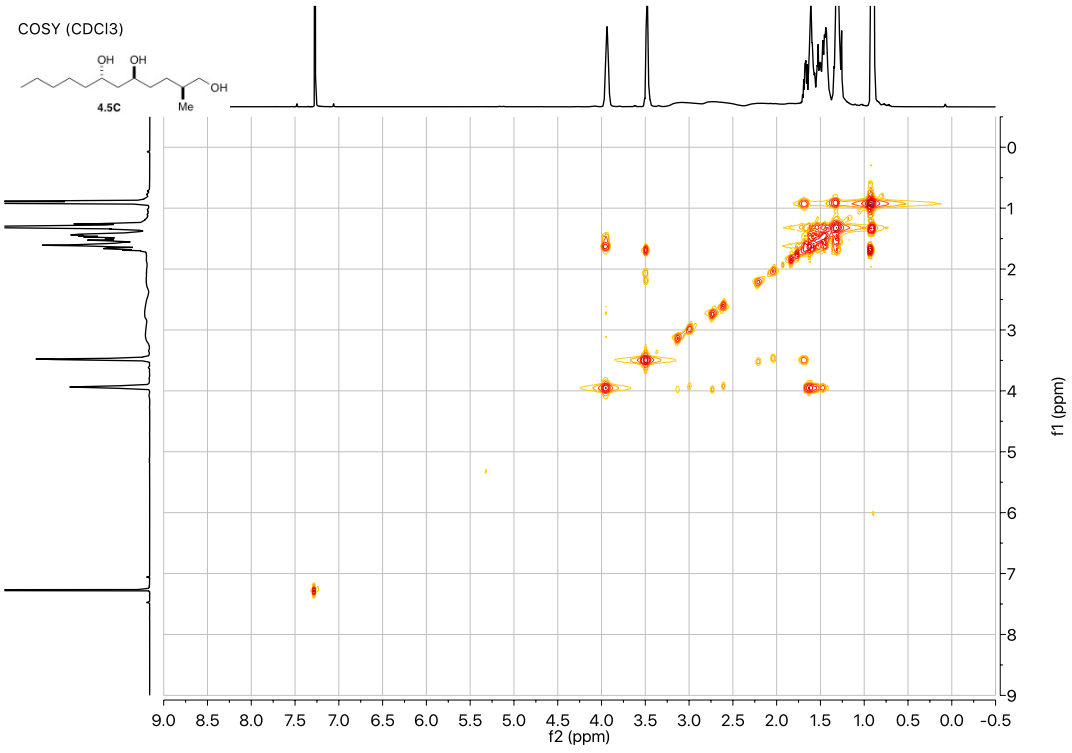
**(2*S*,5*S*,7*S*)-2-methyldodecane-1,5,7-triol ($C_{13}H_{28}O_3$, 3.9.4)**

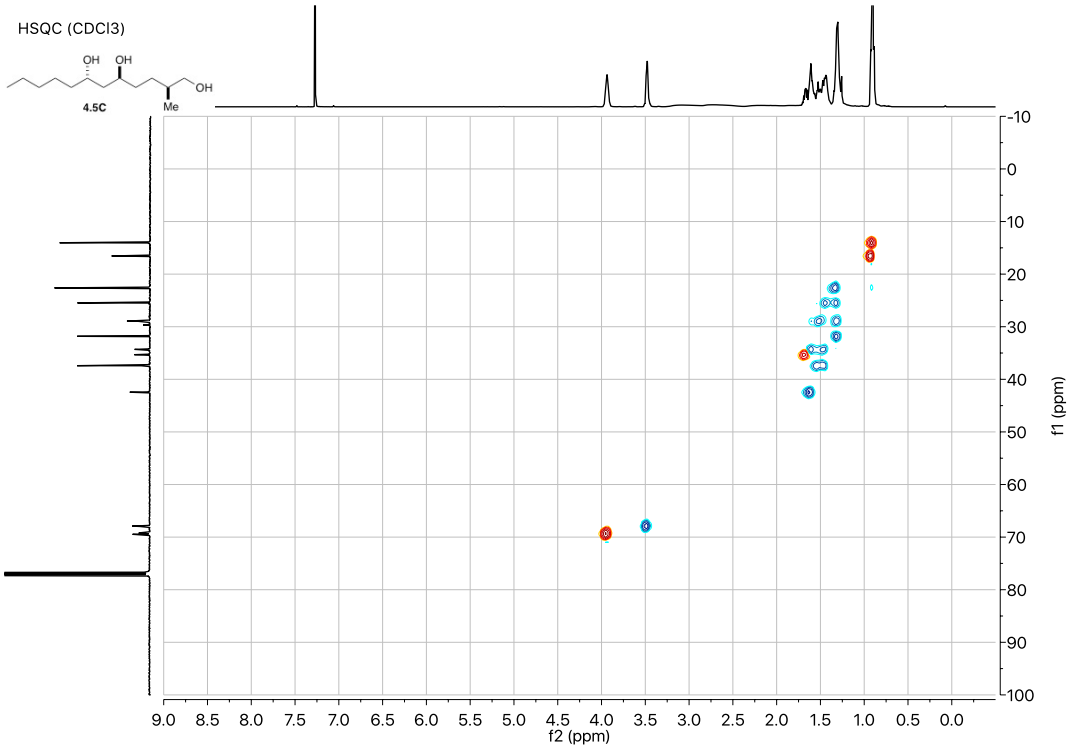



4.5C

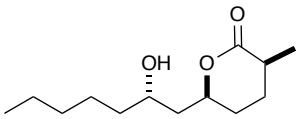



13C NMR (126 MHz, CDCl3)
OH
OH
OH
Me
4.5C
77.25
77.00
76.75
69.47
69.20
67.91
42.45
37.40
35.31
34.31
31.82
28.93
25.47
22.62
16.55
14.03
f1 (ppm)

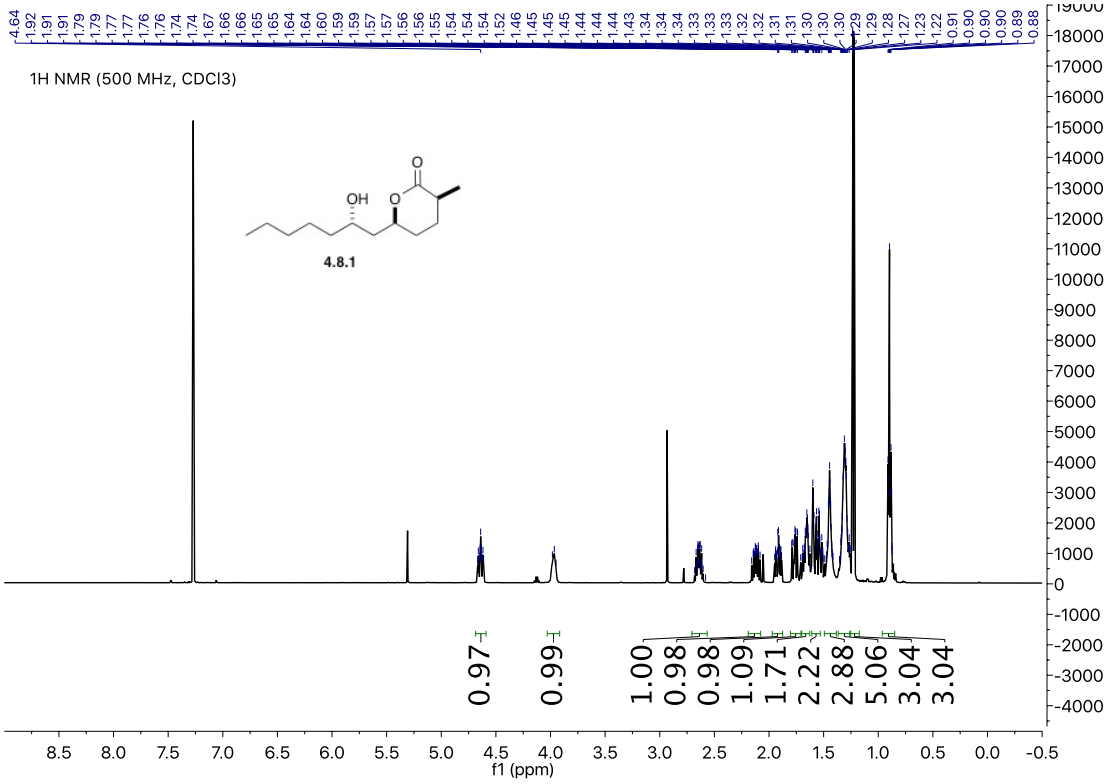

COSY (CDCl3)
OH
OH
OH
Me
4.5C
f2 (ppm)
f1 (ppm)

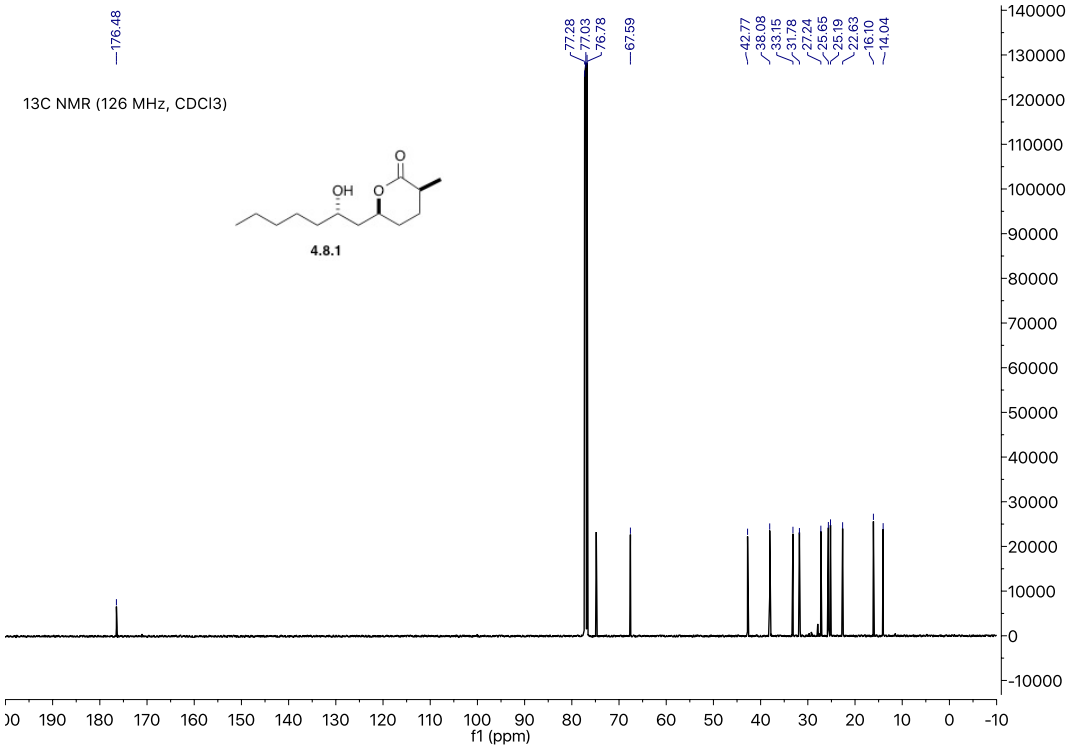

HSQC (CDCl3)
OH
OH
OH
Me
4.5C
-10
0
10
20
30
40
50
60
70
80
90
100
f1 (ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f2 (ppm)

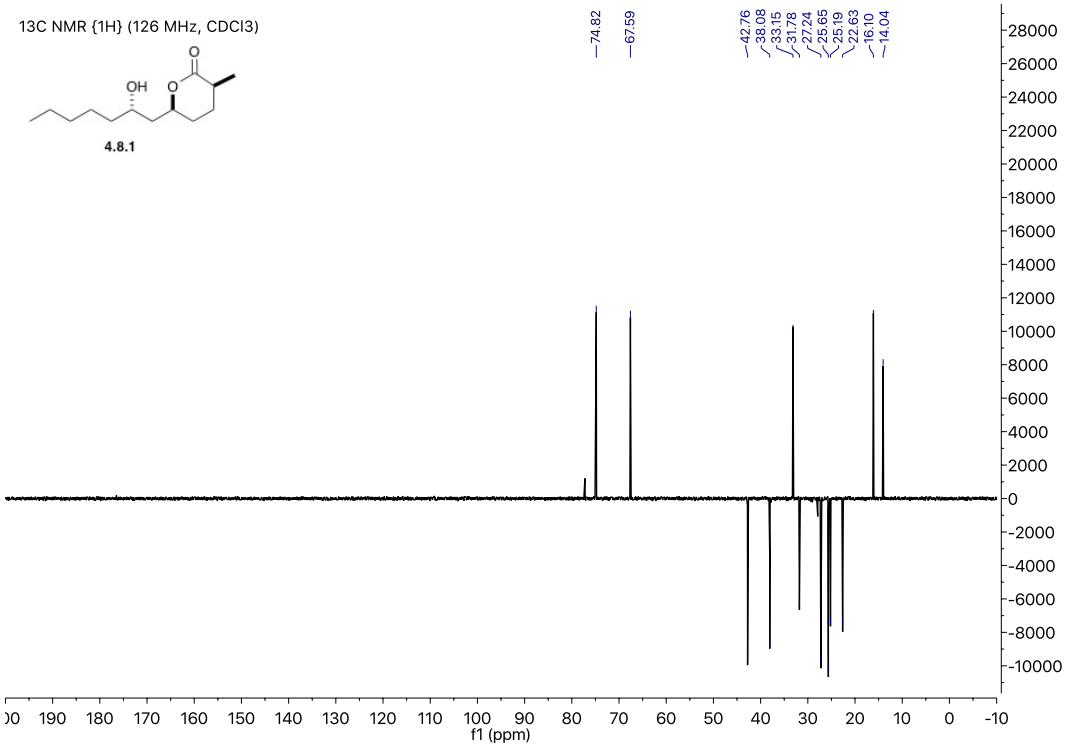
**(3*S*,6*S*)-6-((*S*)-2-hydroxyheptyl)-3-methyltetrahydro-2*H*-pyran-2-one ($C_{13}H_{24}O_3$, 4.8.1)**

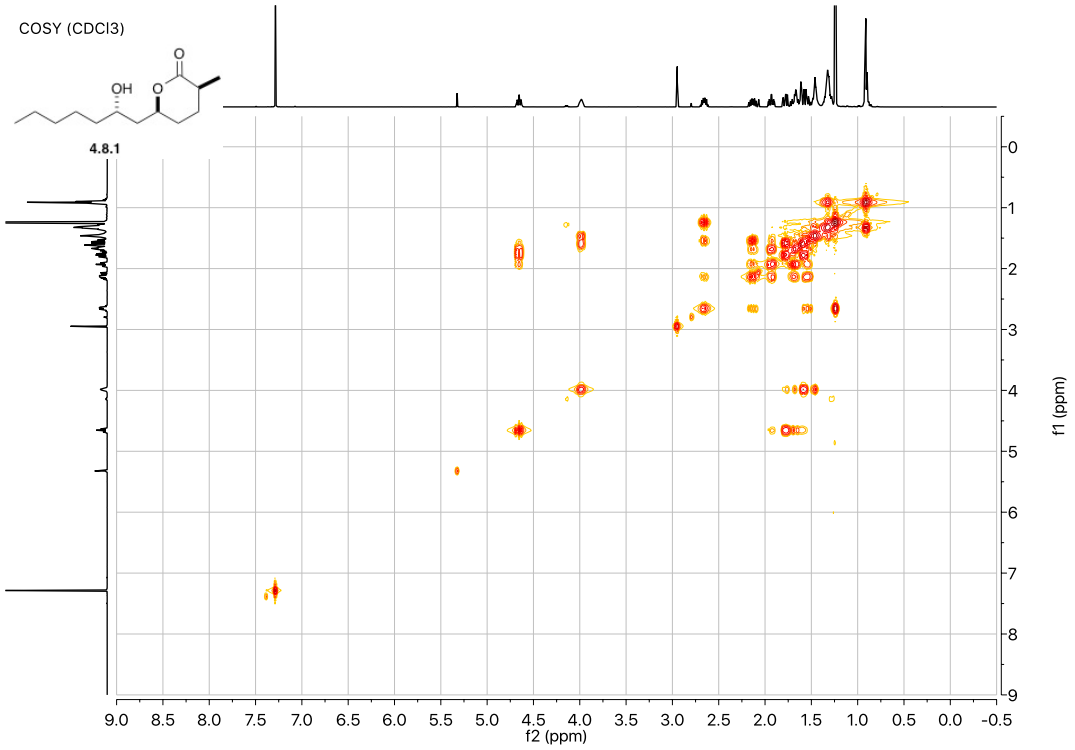


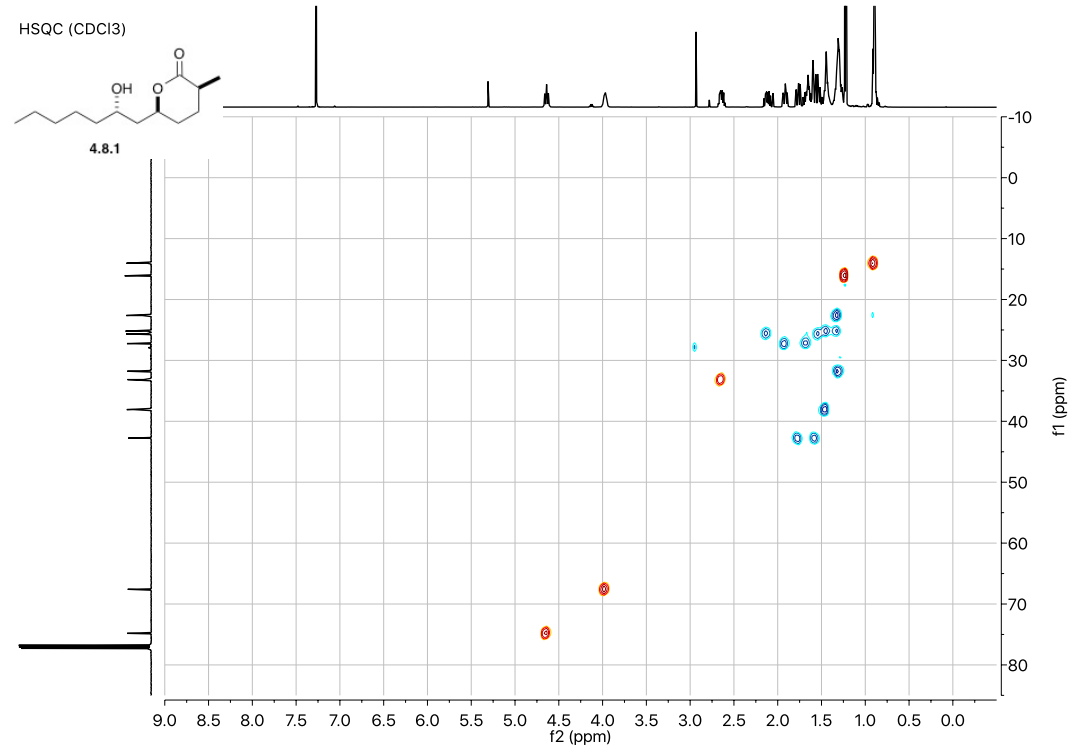

**4.8.1**




13C NMR (126 MHz, CDCl3)
176.48
77.28
77.03
76.78
67.59
42.77
38.08
33.15
31.78
27.24
25.65
25.19
22.63
16.10
14.04
OH
O
O
4.8.1
f1 (ppm)


13C NMR {1H} (126 MHz, CDCl3)
74.82
67.59
42.76
38.08
33.15
31.78
27.24
25.65
25.19
22.63
16.10
14.04
OH
O
O
4.8.1
f1 (ppm)


COSY (CDCl3)
OH
O
O
4.8.1
f2 (ppm)
f1 (ppm)


HSQC (CDCl3)
OH
O
O
4.8.1
f2 (ppm)
f1 (ppm)